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VOLUME 6 1959

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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).

[2] J. R. Goldsmith and D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

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g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (litre), in. (inch) but in^2.

New compounds should be indicated by underlining the name (for italics) at its first mention (including headings) in the experimental section only, and by giving analytical results in the form: (Found: C, 62·9; H, 5·4. $C_{13}H_{12}O_4N$ requires C, 63·2; H 5·3%).

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VOL.
6
1959

LIST OF CONTENTS

VOLUME 6

NUMBER 1

T. URBAŃSKI: A study of the hydrogen bonds between the nitro-group and the hydroxyl or amino-groups in substituted nitroparaffins 1
C. G. MOORE and M. PORTER: The reaction of sulphur and sulphur compounds with olefinic substances—XIII. The mechanism of interaction of sulphur with (+)-limonene 10
NOBUO ITOH and SHIGEHIKO SUGASAWA: Bischler–Napieralski reaction—II. Synthesis of some ketonic *iso*quinolines 16
A. K. GANGULY and T. R. SESHADRI: A study of leucoanthocyanidins of plants—II. (+)Leucocyanidin from the gum of *Butea frondosa* 21
W. VON E. DOERING and H. PRINZBACH: Mechanism of reaction of methylene with the carbon–hydrogen bond. Evidence for direct insertion 24
R. E. WESTON, JR: The magnitude of electronic isotope effects 31
M. NEEMAN, MARJORIE C. CASERIO, JOHN D. ROBERTS and WILLIAM S. JOHNSON: Methylation of alcohols with diazomethane 36
D. H. R. BARTON, P. DE MAYO, G. A. MORRISON and H. RAISTRICK: The constitutions of atrovenetin and of some related herqueinone derivatives 48
J. COMÍN and V. DEULOFEU: Studies on Argentine plants—XVII. The structure of fagarine II . . 63
R. S. MULLIKEN: Bond lengths and bond energies in conjugation and hyperconjugation . . . 68
Preliminary Communication:
M. SAUNDERS and R. W. MURRAY: The reaction of dichlorocarbene with secondary amines . 88
Notes:
C. P. N. NAIR and P. P. PILLAY: Lochnericine—A new alkaloid from *Lochnera rosea* . . 89
J. B. LEE and M. M. EL SAWI: A novel trans-glycosylation reaction 91
Book Reviews:
EUGEN MÜLLER (Editor): "Methoden der Organischen Chemie (Houben-Weyl)" (reviewed by HANS HEYMANN) 94
"Experientia Supplementum VII. XVIth International Congress on Pure and Applied Chemistry" (reviewed by S. P. DATTA) 95
J. FERGUSON: "Bibliotheca Chemica" (reviewed by T. S. WHEELER) 95
Errata 96

NUMBER 2

GJ. STEFANOVIĆ, M. PAVIČIĆ-WOSS, LJ. LORENC and M. LJ. MIHAILOVIĆ: Condensation of isatin with diketones 97
H. S. YANAI and W. N. LIPSCOMB: The structure of ψ-conhydrine 103
M. BALLESTER, C. MOLINET and J. ROSA: The "positive halogen" reaction between benzotrichlorides and potassium iodide. Relevant mechanistic and steric aspects 109
F. WEYGAND, H. SIMON, W. BITTERLICH, J. E. HODGE and B. E. FISHER: Structure of piperidino-hexose-reductone 123
A. FERNEZ et P. J. STOFFYN: Synthèse du 1:6-anhydro-galactose 139
L. H. BRIGGS and B. F. CAIN: Chemistry of the podocarpacae—I. Constituents of the heartwood of *Podocarpus spicatus* 143
L. H. BRIGGS and T. P. CEBALO: Chemistry of the podocarpacae—II. The isolation of genistein from *Podocarpus spicatus* and the constitution of podospicatin 145
A. J. BIRCH and D. NASIPURI: Reaction mechanisms in reductions by metal–ammonia solutions . 148
G. A. RASUWAJEW, L. M. BOBINOWA und V. S. ETLIS: Gewinnung und Eigenschaften einiger titan-organischer Verbindungen 154
L. D. BERGELSON: I. N. Nazarov 1906–1957 161
Book Reviews:
JEAN MATHIEU and ANDRÉ ALLAIS: "Cahiers de Synthèse Organique. Methodes et Tableaux d'Application" (reviewed by LÉO MARION) 166
P. H. GROGGINS (Editor-in-chief): "Unit Processes in Organic Synthesis" (reviewed by HAROLD HARTLEY) 166
W. THEILHEIMER: "Synthetic Methods of Organic Chemistry" (reviewed by D. H. R. BARTON) . 167
J.-P. MATHIEU and G. OURISSON: "Selected Constants—Optical Rotatory Power. II. Triterpenoids" (reviewed by R. C. COOKSON) 168

NUMBER 3

T. R. SESHADRI: Recent developments in the chemistry of flavonoids 169
F. KORTE, J. FALBE und A. ZSCHOCKE: α-Hydroxyalkyliden-Lacton-Umlagerung—IX. Synthese des D,L-Iridomyrmecins und verwandter bicyclischer Lactone 201
K. J. CLARK, G. I. FRAY, R. H. JAEGER and Sir ROBERT ROBINSON: Synthesis of D- and L-*iso*iridomyrmecin and related compounds 217
T. L. V. ULBRICHT: Synthesis with pyrimidine-lithium compounds 225

C. Mechelynck-David et P. J. C. Fierens: Etudes cinétiques des réactions de solvolyse de chlorures d'α-phenylethyle substitués. Equations de Hammett, Winstein–Grünwald et Tommila . . 232
R. Huisgen und H. Ott: Die Konfiguration der Carbonestergruppe und die Sondereigenschaften der Lactone 253
Book Review:
John T. Edsall and Jeffries Wyman: "Biophysical Chemistry Vol. 1. Thermodynamics, Electrostatics and the Biological Significance of the Properties of Matter (reviewed by S. P. Datta) . 268

NUMBER 4

H. J. E. Loewenthal: Selective reactions and modifications of functional groups in steroid chemistry 269
Gj. Stefanović, Lj. Lorenc, R. I. Mamuzić and M. Lj. Mihailović: Anhydrobiisatic acid. 6:12-Oxa-5:6:11:12-tetrahydrophenhomazine-6:12-dicarboxylic acid 304
P. K. Grover and T. R. Seshadri: Constitution of pinastric acid 312
F. L. Allen, P. Koch and H. Suschitzky: Heterocyclic fluorine compounds—III. Monofluoroxanthones 315
A. H. Beckett, N. J. Harper, A. D. J. Balon and T. H. E. Watts: Stereochemistry of the reduction of tropinone 319
N. R. Ayyangar, B. S. Joshi and K. Venkataraman: Anthraquinone and anthrone series—XXIII. The non-identity of 1:3:8-trihydroxy-2-hydroxymethyl anthraquinone with versicolorin and a synthesis of damnacanthol and damnacanthal 331
A. Streitwieser, Jr., J. R. Wolfe, Jr. and W. D. Schaeffer: Stereochemistry of the primary carbon—X. Stereochemical configurations of some optically active deuterium compounds . . 338
W. Metlesics, F. Wessely und H. Budzikiewicz: Dienon-Phenol-Umlagerung von Chinolen—II. Beitrag zur Klärung des Reaktionmechanismus 345
E. Clar: Asymmetric annellation effects—II. 355
E. Clar, C. T. Ironside and M. Zander: Asymmetric and symmetric annellation effects—III. Benzocoronenes 358
Books Received 364
Subject index to Volumes 1 to 3 of Tetrahedron

AUTHOR INDEX

(B) denotes Book Review

Allen, F. L. p. 315
Ayyangar, N. R. p. 331
Ballester, M. p. 109
Balon, A. D. J. p. 319
Barton, D. H. R. pp. 48, 167(B)
Beckett, A. H. p. 319
Bergelson, L. D. p. 161
Birch, A. J. p. 148
Bitterlich, W. p. 123
Bobinowa, L. D. p. 154
Briggs, L. H. pp. 143, 145
Budzikiewicz, H. p. 345
Cain, B. F. p. 143
Caserio, Marjorie C. p. 36
Cebalo, T. P. p. 145
Clar, E. pp. 355, 358
Clark, K. J. p. 217
Comín, J. p. 63
Cookson, R. C. p. 168 (B)
Datta, S. P. pp. 95 (B), 268 (B)
Deulofeu, V. p. 63
Doering, W. von E. p. 24
Etlis, V. S. p. 154
Falbe, J. p. 201
Fernez, A. p. 139
Fierens, P. J. C. p. 232
Fisher, B. E. p. 123
Fray, G. I. p. 217
Ganguly, A. K. p. 21
Grover, P. K. p. 312
Harper, N. J. p. 319
Hartley, Harold p. 166 (B)
Heymann, Hans p. 94 (B)
Hodge, J. E. p. 123
Huisgen, R. p. 253
Ironside, C. T. p. 358
Itoh, Nobuo p. 16
Jaeger, R. H. p. 217
Johnson, William S. p. 36
Joshi, B. S. p. 331
Koch, P. p. 315
Korte, F. p. 201
Lee, J. B. p. 91
Lipscomb, W. N. p. 103
Loewenthal, H. J. E. p. 269
Lorenc, Lj. pp. 97, 304
Mamuzić, R. I. p. 304
Marion, Léo p. 166 (B)
Mayo, P. de p. 48
Mechelynck-David, C. p. 232
Metlesics, W. p. 345
Mihailović, M. Lj. pp. 97, 304
Molinet, C. p. 309
Moore, C. G. p. 10
Morrison, G. A. p. 48
Mulliken, R. S. p. 68
Murray, R. W. p. 88
Nair, C. P. N. p. 89
Nasipuri, D. p. 148
Neeman, M. p. 36
Ott, H. p. 253
Pavičić-Woss, M. p. 97
Pillay, P. P. p. 89
Porter, M. p. 10
Prinzbach, H. p. 24
Raistrick, H. p. 48
Rasuwajew, G. A. p. 154
Roberts, John D. p. 36
Robinson, Robert p. 217
Rosa, J. p. 109
Saunders, M. p. 88
Sawi, M. M. el p. 91
Schaeffer, W. D. p. 338
Seshadri, T. R. pp. 21, 169, 312
Simon, H. p. 123
Stefanović, Gj. pp. 97, 304
Stoffyn, P. J. p. 139
Streitwieser, Jr., A. p. 338
Sugasawa, Shigehiko p. 16
Suschitzky, H. p. 315
Ulbricht, T. L. V. p. 225
Urbański, T. p. 1
Venkataraman, K. p. 331
Watts, T. H. E. p. 319
Wessely, F. p. 345
Weston, Jr., R. E. p. 31
Weygand, F. p. 123
Wheeler, T. S. p. 95(B)
Wolfe, Jr., J. R. p. 338
Yanai, H. S. p. 103
Zander, M. p. 358
Zschocke, A. p. 201

VOL.
6
1959

VO
6
19

Tetrahedron, 1959, Vol. 6, pp. 1 to 9. Pergamon Press Ltd. Printed in Northern Ireland

A STUDY OF THE HYDROGEN BONDS BETWEEN THE NITRO-GROUP AND THE HYDROXYL OR AMINO-GROUPS IN SUBSTITUTED NITROPARAFFINS

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(*Received* 10 *July* 1958)

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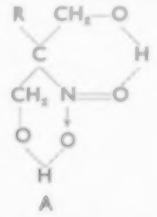
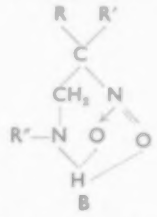
Abstract—The ultra-violet absorption spectra of many nitro paraffin derivatives containing hydroxyl and or amino groups, do not show a maximum (260–270 mμ) typical of the nitro group. This is attributed to the formation of six-membered chelate rings by internal hydrogen bonds between the nitro and hydroxyl or amino groups. *Two* hydroxyl groups or *one* secondary amino group are necessary to transform the normal maximum of the nitro group into a bend. This is considered as new evidence for the mainly electrostatic nature of the hydrogen bond. Hydrogen bonds between nitro and hydroxyl or amino groups also produce a bathochromic effect; the corresponding maxima or shoulders being shifted towards longer waves (270–285 mμ).

THE effect of the hydrogen bond on electronic spectra has recently been reviewed.[1] Morton and Stubbs,[2] proved in the case of hydroxybenzaldehydes that both inter- and intra-molecular bonds, and association between solute and solvent can produce a shift of the benzenoid ultra-violet absorption bands towards longer wavelengths. The degree of shift for different isomers depends on the strength of the bonds. Burawoy *et al.*[3] have confirmed this by comparing electronic spectra of substituted phenol and anisole. The abnormal ultra-violet absorption spectra[4] of nitro paraffin derivatives containing hydroxyl and or amino groups are considered to be due to the formation of six-membered chelate rings[4,5] by internal hydrogen bonds between the nitro group and the hydroxyl or amino group. Two hydroxyl groups or one amino group forming the chelate rings (formulae A and B) are required to transform the normal maximum of the nitro group into a shoulder; the presence of a single hydroxyl



A



B

group and consequent hydrogen bonding has a bathochromic effect, but does not appreciably alter the shape of the ultra-violet spectra. The stronger electron repelling properties of the amino as compared with the hydroxyl group, together with the

[1] *IUPAC Symposium on Hydrogen Bond*, Ljubljana (1957). W. F. Forbes and J. F. Templeton, *Chem. & Ind.* **77**, (1957).
[2] R. A. Morton and A. L. Stubbs, *J. Chem. Soc.* 1347 (1940).
[3] A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.* 2310 (1952). A. Burawoy, M. Cais, J. T. Chamberlain, F. Liversedge and A. R. Thompson, *Ibid.* 3721, 3727 (1955).
[4] T. Urbański, *Bull. Acad. Pol. Sci.* Cl. III, **1**, 239 (1953).
[5] T. Urbański and D. Ciecierska, *Roczn. Chem.* **29**, 11 (1955); T. Urbański, *Bull Acad. Pol. Sci.* Cl.III **2**, 393 (1954); *Roczn. Chem.* **29**, 375 (1955); T. Urbański, *IUPAC Symposium on Hydrogen Bond*, Ljubljana (1957).

1

electron attracting properties of the nitro group are considered evidence supporting the view that the hydrogen bond is mainly electrostatic.

All compounds investigated produce a strong absorption band near 200 mμ. This may be produced by single bonded atoms or groups with single bonds (auxochroms), such as —O— , >N— and —C—C—.[6] The existence of hydrogen bonds between hydroxyl or amino groups and a nitro group has been confirmed by infra-red absorption spectra.[7]

EXPERIMENTAL

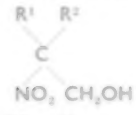
In the present paper, previously published and unpublished results are given. A quartz Beckman spectrophotometer (model DU) with hydrogen lamp and 1–4 mμ beam width was used. Measurements were made every 5 mμ on aqueous or ethyl alcohol solutions of the compounds.

The names or structural formulae of all compounds are:

Nitroparaffins

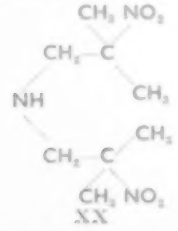
I Nitromethane
II Nitroethane
III 1-Nitropropane
IV 2-Nitropropane
V 1-Nitro-*n*-butane
VI 1-Nitro*iso*butane
VII 1-Nitro-*n*-pentane
VIII 1-Nitro-*n*-hexane

Nitroalcohols



IX $R^1 = R^2 = H$
X $R^1 = R^2 = CH_2OH$
XI $R^1 = CH_3$, $R^2 = H$
XII $R^1 = CH_3$, $R^2 = CH_2OH$
XIII $R^1 = C_2H_5$, $R^2 = H$
XIV $R^1 = C_2H_5$, $R^2 = CH_2OH$
XV $R^1 = R^2 = CH_3$
XVI $R^1 = C_3H_7$, $R^2 = CH_2OH$
XVII $R^1 = iso\text{-}C_3H_7$, $R^2 = CH_2OH$
XVIII $R^1 = C_4H_9$, $R^2 = CH_2OH$
XIX $R^1 = C_5H_{11}$, $R^2 = CH_2OH$

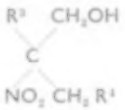
Aminonitro compound



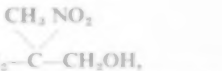
XX

XXI hydrochloride of XX

Aminonitroalcohols

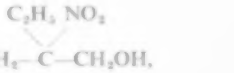


XXII $R^3 = C_2H_5$, $R^4 = NH_2$, hydrochloride
XXIII $R^3 = C_3H_7$, $R^4 = NH_2$, hydrochloride
XXIV $R^3 = C_3H_7$, $R^4 = NHCH_3$, hydrochloride
XXV $R^3 = C_3H_7$, $R^4 = NHC_2H_5$, hydrochloride
XXVI $R^3 = iso\text{-}C_3H_7$, $R^4 = NH_2$, hydrochloride
XXVII $R^3 = C_4H_9$, $R^4 = NH_2$, hydrochloride
XXVIII $R^3 = C_4H_9$, $R^4 = NHCH_3$, hydrochloride
XXIX $R^3 = CH_3$,

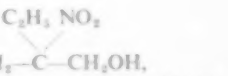


hydrochloride

XXX $R^3 = C_2H_5$,

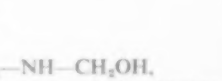


XXXI $R^3 = C_2H_5$,



hydrochloride

XXXII $R^3 = C_2H_5$,

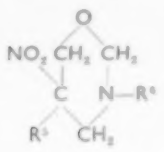


hydrochloride

[6] E. A. Braude, *Ann. Rep. Progr. Chem.* **42**, 105 (1945).

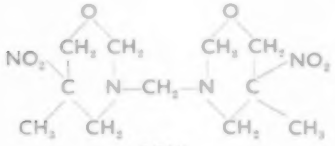
[7] T. Urbański, *Bull. Acad. Polon. Sci.* Cl. III. **4**, 87, 381 (1956); *Roczn. Chem.* **31**, 37 (1957).

1:3-Tetrahydro-oxazine derivatives



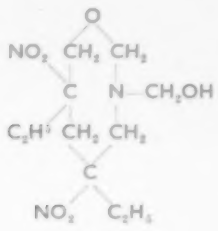
XXXIII $R^5 = C_2H_5$, $R^6 = H$, hydrochloride
XXXIV $R^5 = C_2H_5$, $R^6 = CH_3$, hydrochloride
XXXV $R^5 = C_2H_5$, $R^6 = (CH_3)_2\,I^{\ominus}$

XXXVI $R^5 = C_2H_5$, $R^6 = CH_2{-}C{-}CH_2OH$
XXXVII $R^5 = C_3H_7$, $R^6 = H$, hydrochloride
XXXVIII $R^5 = C_3H_7$, $R^6 = CH_3$, hydrochloride
XXXIX $R^5 = C_3H_7$, $R^6 = C_2H_5$, hydrochloride
XL $R^5 = iso\text{-}C_3H_7$, $R^6 = H$, hydrochloride
XLI $R^5 = iso\text{-}C_3H_7$, $R^6 = CH_3$, hydrochloride
XLII $R^5 = iso\text{-}C_3H_7$, $R^6 = C_2H_5$, hydrochloride
XLIII $R^5 = C^4H_9$, $R^6 = H$, hydrochloride
XLIV $R^5 = C_4H_9$, $R^6 = CH_3$, hydrochloride
XLV $R^5 = C_4H_9$, $R^6 = C_2H_5$, hydrochloride



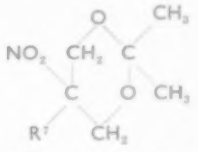
XLVI

1-Oxa-3-aza-cycloöctane derivative



XLVII

1:3-Dioxane derivatives



XLVIII $R^7 = CH_3$
XLIX $R^7 = CH_2OH$

All compounds, from (IX) onwards have been prepared according to the literature; compounds (IX–XIX) according to Vanderbildt and Hass[8] and Urbański and Chylińska.[9]

All other compounds were prepared according to methods described by other workers and the present author.[10]

In addition to the compounds containing a nitro group, the absorption spectra of two derivatives of 1:3-tetrahydro-oxazine without a nitro group, have also been

[8] B. M. Vanderbildt and H. B. Hass, *Industr. Engng. Chem.* **32**, 34 (1940).

[9] T. Urbański and B. Chylińska, *Roczn. Chem.* **31**, 695 (1957).

[10] E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochyński, A. T. Thomas and T. Urbański, *J. Chem. Soc.* 924 (1947); J. K. N. Jones and T. Urbański, *Ibid.* 1766 (1949); T. Urbański and S. Malinowski, *Roczn. Chem.* **25**, 183 (1951); T. Urbański and E. Lipska, *Ibid.* **26**, 182 (1952); T. Urbański and H. Piotrowska, *Bull. Acad. Pol. Sci.* Cl. III, **3**, 389 (1955); *Roczn Chem.* **29**, 379 (1955); **31**, 553 (1957); T. Urbański and J. Kolesińska, *Ibid.* **29**, 392 (1955); T. Urbański and D. Gürne, *Bull. Acad. Pol. Sci.* Cl. III. **3**, 175 (1955); **4**, 221 (1956); *Roczn. Chem.* **31**, 855, 869 (1957); T. Urbański, H. Dabrowska, B. Lesiowska, H. Piotrowska, *Ibid.* **31**, 687 (1957).

VOL. 6 1959

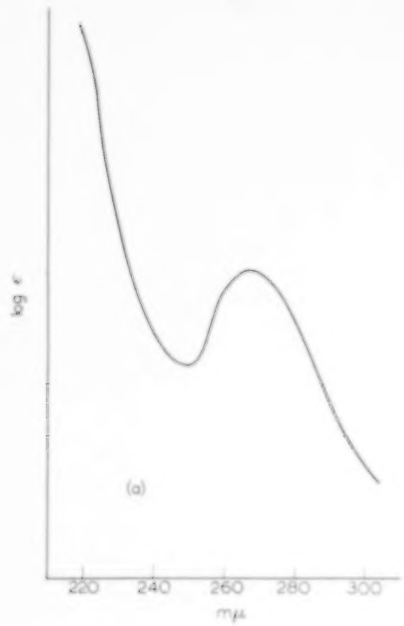


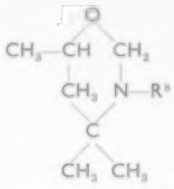
FIG. 1. Curve (a)—with a strong maximum.

FIG. 2. Curve (b)—with a very weak maximum, or a very strong shoulder.

FIG. 3. Curve (c)—with a clear bend.

FIG. 4. Curve (d)—with a very weak bend.

examined. They are compounds (L) and (LI), which have been



L $R^5 = H$, hydrochloride
LI $R^5 = CH_3$, hydrochloride

prepared according to Kohn.[11,12]

All absorption curves can be classified in four types (Fig. 1–4)

All numerical results are tabulated (Tables 1 and 2)

TABLE 1

Substance	Solvent	Minimum			Maximum			$\Delta\varepsilon$	Shape of the curve
		wave-length (mμ)	log ε	ε	wave-length (mμ)	log ε	ε		
I	Alcohol	250	1·50	31·7	260	1·59	39·1	7·4	A
II	Alcohol	250	1·54	34·3	260	1·63	42·3	8·0	A
III	Alcohol	250	1·07	11·8	270	1·59	39·3	27·5	A
IV	Alcohol	250	1·58	37·7	260	1·66	45·7	8·0	A
V	Alcohol	247	1·17	15·0	272	1·40	25·4	10·4	A
VI	Alcohol	245	2·05	112·5	255	2·09	121·7	9·2	A
VII	Alcohol	250	1·40	24·9	270	1·51	32·2	7·3	A
VIII	Alcohol	248	1·48	30·2	261	1·55	35·7	5·5	A
IX	Alcohol	258	1·43	27·0	270	1·45	28·1	1·1	A
X	Alcohol	265	1·53	33·6	275	1·53	33·6	0·0	B
	Water		a bend		c282	1·60	40·1	—	C
XI	Alcohol	250	1·24	17·4	275	1·49	31·1	13·7	A
XII	Alcohol	262	1·42	26·4	275	1·52	32·9	6·5	A
	Water	268	1·54	34·7	275	1·54	34·7	0·0	B
XIII	Alcohol	251	1·28	18·9	279	1·47	29·4	10·5	A
XIV	Alcohol		a bend		c280	1·61	40·4	—	C
	Water		a bend		c285	1·46	29·3	—	C
XV	Alcohol	252	1·23	16·9	278	1·49	31·0	14.1	A
	Water	255	1·28	17·8	280	1·47	29·8	12.0	A
XVI	Water		a bend		c280	1·57	37·2	—	C
XVII	Water		a bend		c275	1·70	50·7	—	C
XVIII	Water		a weak bend		c280	1·59	38·9	—	D
XIX	Water		a bend		c275	1·62	41·5	—	C

[11] M. Kohn, *Monatshefte* **25**, 135, 817, 830, 850 (1904);

[12] T. Urbański and B. Gac-Chylińska, *Roczn. Chem.* **30**, 185 (1956).

TABLE 2

Substance	Solvent	Minimum			Maximum			$\Delta\varepsilon$	Shape of the curve
		wave-length (mμ)	log ε	ε	wave-length (mμ)	log ε	ε		
XX	Alcohol	250	2·87	741	256	2·90	794	53	A
XXI	Water	a bend c			280	1·85	70·7	—	C
XXII	Water	a bend			c280	1·64	43·9	—	C
XXIII	Water	a weak bend			c275	1·81	65·3	—	D
XXIV	Water	a weak bend			c280	1·55	35·8	—	D
XXV	Water	a bend			c285	1·52	33·2	—	C
XXVI	Water	a bend			c275	1·72	52·8	—	C
XXVII	Water	a bend			c272	1·62	41·8	—	C
XXVIII	Water	a weak bend			c280	1·66	45·7	—	D
XXIX	Water	a bend			c250	2·79	623	—	C
XXX	Water	a bend			c270	2·73	540	—	C
XXXI	Alcohol	a bend			c265	2·52	331	—	C
XXXII	Water	a bend			c260	2·48	302	—	C
XXXIII	Water	260	1·78	60·4	272	1·81	64·3	3·9	A
XXXIV	Water	255	1·57	37·3	270	1·61	40·3	3·0	A
XXXV	Water	272	1·60	39·8	278	1·60	39·8	0·0	B
XXXVI	Alcohol	248	2·64	437	260	2·68	477	40	A
XXXVII	Water	256	1·73	53·7	275	1·82	66·1	12·4	A
XXXVIII	Water	255	1·52	33·0	273	1·58	38·2	5·2	A
XXXIX	Water	245	1·98	95·9	260	1·98	95·9	0·0	B
XL	Water	257	1·56	36·5	275	1·61	40·9	4·4	A
XLI	Water	252	1·48	30·2	277	1·65	44·4	14·2	A
XLII	Water	255	1·44	27·9	280	1·64	43·8	16·1	A
XLIII	Water	255	1·49	30·9	275	1·55	35·3	4·4	A
XLIV	Water	255	1·53	34·1	275	1·60	40·2	6·1	A
XLV	Water	262	1·59	39·0	270	1·60	39·8	0·8	A-B
XLVI	Alcohol	250	2·77	593	262	2·80	631	38	A
XLVII	Alcohol	250	2·63	431	260	2·67	470	39	A
XLVIII	Alcohol	260	1·29	19·4	278	1·40	24·9	5·5	A
XLIX	Alcohol	265	1·18	15·1	284	1·34	21·9	6·8	A
L	Water	a very weak bend			c240	0·8	6·3	—	D
LI	Water	a very weak bend			c230	1·4	25·1	—	D

DISCUSSION

New results described in this paper confirm fully previous observations and all former statements have been confirmed. In addition, a few more conclusions may be drawn.

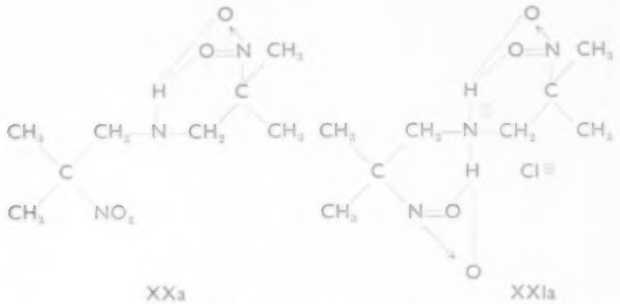
Dinitrocompounds: (XX, XXIX–XXXII, XXXVI, XLVI and XLVII) are composed of two molecules of nitro paraffins; they are distinguished by their high extinction coefficients.

In (XX) one nitro group may be bonded by a bifurcated hydrogen bond and the second "free" (XXa), or both nitro groups may be partially bonded (XXb).

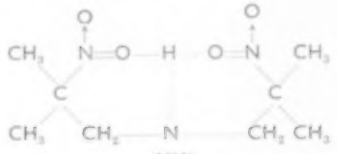
Compound (XX), shows a relatively strong extinction (c.800) at the maximum characteristic of the nitro group, the shape of the absorption curve (a) agreeing with the structure (XXa). The hydrochloride (XXI) shows a much lower extinction (of the order of 70) at the bend [curve (c)] and no maximum of the nitro group (XXIa).

It is suggested that (XXa) with two nitro groups, one of which is "free", is responsible for the high extinction. In contrast, fully bonded two nitro groups (XXIa) give a relatively low extinction, although it is higher than in the case of the compounds with one nitro group.

The compounds with two nitro groups (XXIX, XXX, XXXI and XXXII) in form of hydrochlorides with sufficient hydrogen atoms to transform the maximum of the

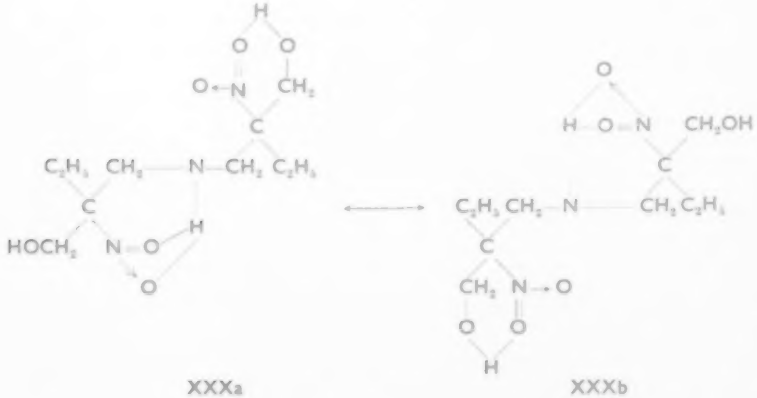


XXa XXIa



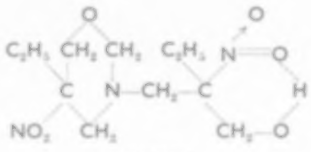
XXb

nitro group, show a relatively high extinction of the order of 300 to 600 (lower than XX). Mesomeric structures, (e.g. XXXa and XXXb), could be suggested for this type of



XXXa XXXb

compound. Compounds with two unbonded or partially bonded nitro groups (XXXVI, XLVI, XLVII—a typical structure being XXXVIa) also give a high extinction.



XXXVIa

Aminonitroalcohols with relatively long chain molecules of the type (XXIX–XXXII) show a higher extinction than aminonitroalcohols with one nitro group (XXII–XXVIII).

Ring compounds with: (i) a long side chain (XXXVI); (ii) two 1:3-oxazine rings, each containing a nitro group (XLVI); (iii) a larger (eight member) ring with two nitro groups (XLVII), all give a higher extinction coefficient than simpler 1:3-oxazine derivatives (XXXIII, XXXIV, XXXVII–XLV).

1:3-*Tetrahydro-oxazine compounds* with a 5-nitro-1:3-tetrahydro-oxazine ring give a clear maximum characteristic of a nitro group. No hydrogen bond is possible between the nitro group and N-hydrogen in compounds (XXXIII, XXXVII, XL, XLIII), the distance between oxygen atoms and N-hydrogen being larger than 3 Å.

The N-ethyl groups (XXXIX and XLV) produce a steric influence upon the nitro group shown by weakening of the absorption maximum, curve (b). The same applies to the quaternary iodide (XXXV) where two N-methyl groups and the iodine ion are present. In contrast, it is difficult to explain the lack of the effect of N-ethyl in (XLII).

Compounds with a 1:3-oxazine ring and no nitro group (XL and XLI) show a strong maximum in the proximity of 200 mμ, which seems to be characteristic of all substances described in the present paper. The lack of a chromophore in these molecules may be responsible for the very small extinction coefficient in the absorption curves of (XL) and (XLI) at 240 and 230 mμ respectively.

The absorption spectra of 1-nitrobutane (V) and 1-nitro*iso*butane (VI) and also those of their respective diols (XVI and XVII), conform to the general rule that branched alkyls produce a higher extinction coefficient than straight chain ones.[13] This rule, however, does not apply to some 1:3-oxazine derivatives, (XXXVII and XXXIX) from 1-nitrobutane possessing a slightly higher coefficient than the corresponding derivatives (XL and XLII) of 1-nitro*iso*butane.

Bathochromic effect

When internal hydrogen bonds are present the maximum produced by the nitro group or the bend corresponding to this maximum is shifted towards longer wavelengths.

This bathochromic effect can be observed when comparing maxima in nitro paraffins with maxima or bends in the corresponding nitro alcohols. Thus, when nitromethane (I, max 260 mμ); was converted to a monohydroxylic alcohol (IX) the maximum was shifted to 270 mμ; and when three alcoholic groups were introduced, (the triol X) the maximum was transformed into a bend at c. 275 mμ (all in alcoholic

[13] A. E. Fehnel and M. Cormack, *J. Amer. Chem. Soc.* **71**, 84 (1949).

solution). In the case of nitroethane (II) the maximum, 260 mμ was shifted to 275 mμ in the monol (XI), and the same wavelength was found for the bend in the case of the diol (XII).

A comparison of nitro paraffins and nitro alcohols with the same number of carbon atoms leads to the same conclusion. Alcohol (IX) has the maximum at 270 mμ, i.e. at a higher wavelength than nitroethane.

A similar shifting was observed in the case of 1-nitropropane (III, 270 mμ) and the corresponding monol (XIII, max 279 mμ) and diol (XIV, bend at c. 280 mμ). 2-Nitropropane (IV) has the maximum at 260 mμ and the alcohol (XV) gives a maximum at 278 mμ. 2-Nitropropane should also be compared with 2-nitropropane-1-ol (XI) which shows an absorption band at a longer wavelength (275 mμ). It should be pointed out, that although one hydroxyl group is not sufficient to transform a maximum into a bend, it can produce a shifting of the maximum of the nitro group. All higher nitro paraffins (V–VII) show the same type of shifting from 272, 255, 270, 261 mμ to 280, 275, 280, 275 mμ respectively after being transformed into the corresponding diols (XVI–XIX).

The same wavelengths (272–285 mμ) of the bends corresponding to the bonded nitro group was also found in amino-nitro alcohols derived from nitro paraffins.

Acknowledgements—The author is much indebted to Dr. (Mrs.) J. Swietoslawska, Miss D. Ciecierska and Miss B. Gorczyńska for examining the ultra-violet absorption spectra. His thanks are also due to all his collaborators who prepared the substances described in the present paper.

VOL. 6 1959

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THE REACTION OF SULPHUR AND SULPHUR COMPOUNDS WITH OLEFINIC SUBSTANCES—XIII*

THE MECHANISM OF INTERACTION OF SULPHUR WITH (+)-LIMONENE

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The British Rubber Producers' Research Association,
Welwyn Garden City, Herts, England

Abstract—The reaction of sulphur with (+)-limonene (I) to give the hydrocarbons (II) and (III), and the cyclic sulphides (+)-(IV), (−)-(V), and optically inactive (VI), as demonstrated by Weitkamp,[1–3] is shown to be uniquely consistent with a recently advanced polar mechanism of olefinic sulphuration.[3,4]

WEITKAMP[1–3] has shown that reaction of sulphur with (+)-limonene (I) at 140–170°C yields *p-iso*propenyltoluene (II), *p*-cymene (III); the cyclic sulphides (+)-(IV), (−)-(V), and optically inactive (VI); and an unresolved "limonene" polysulphide. The stereochemical relationships between the reactant (I) and the cyclic sulphides (IV)–(VI) were convincingly established, but no detailed or acceptable mechanistic explanation was offered for the formation of the various products.

I

II

III

IV

V

VI

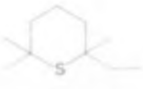
The sulphuration of (I) to give (II)–(VI) is analogous to the sulphuration of 2:6-dimethylocta-2:6-diene (VII) to give (VIII)–(XII),[4] products which are explicable

VII

VIII

IX

X



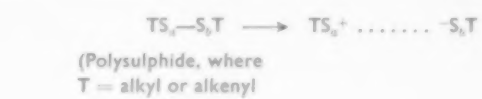
XI

XII

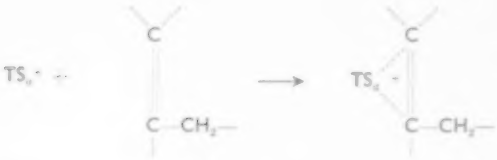
* Part XII, L. Bateman, R. W. Glazebrook and C. G. Moore, *J. Polymer Sci.* In press.

[1] A. W. Weitkamp, *Preprints of papers presented before the Division of Petroleum Chemistry, San Francisco Meeting*, 13–18 April, p. 253. American Chemical Society (1958).
[2] A. W. Weitkamp, *Preprints of papers presented before the Division of Petroleum Chemistry, San Francisco Meeting*, 13–18 April, p. 259. American Chemical Society (1958).
[3] A. W. Weitkamp, *Preprints of papers presented before the Division of Petroleum Chemistry, San Francisco Meeting*, 13–18 April, p. 263. American Chemical Society (1958).
L. Bateman, R. W. Glazebrook and C. G. Moore, *J. Chem. Soc.* 2846 (1958).

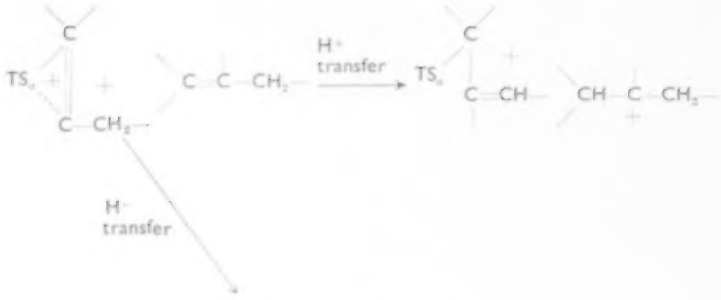
on the basis of a recently proposed *polar* mechanism,[5,6] the general features of which are given by reactions (1)–(7):



(1)

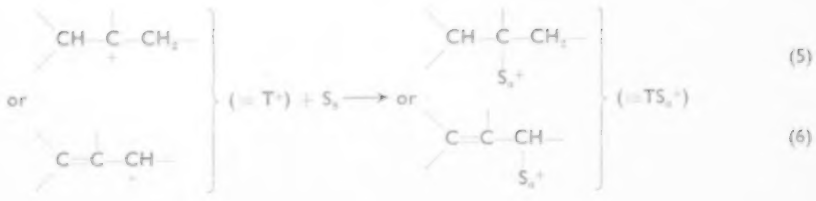


(2)



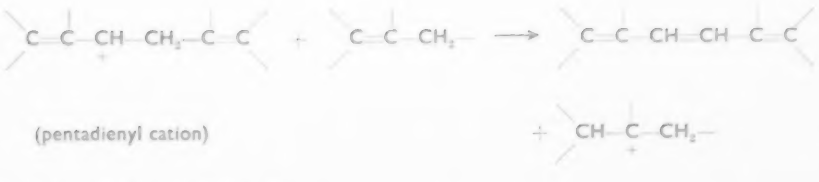
(3)

(4)



(5)

(6)

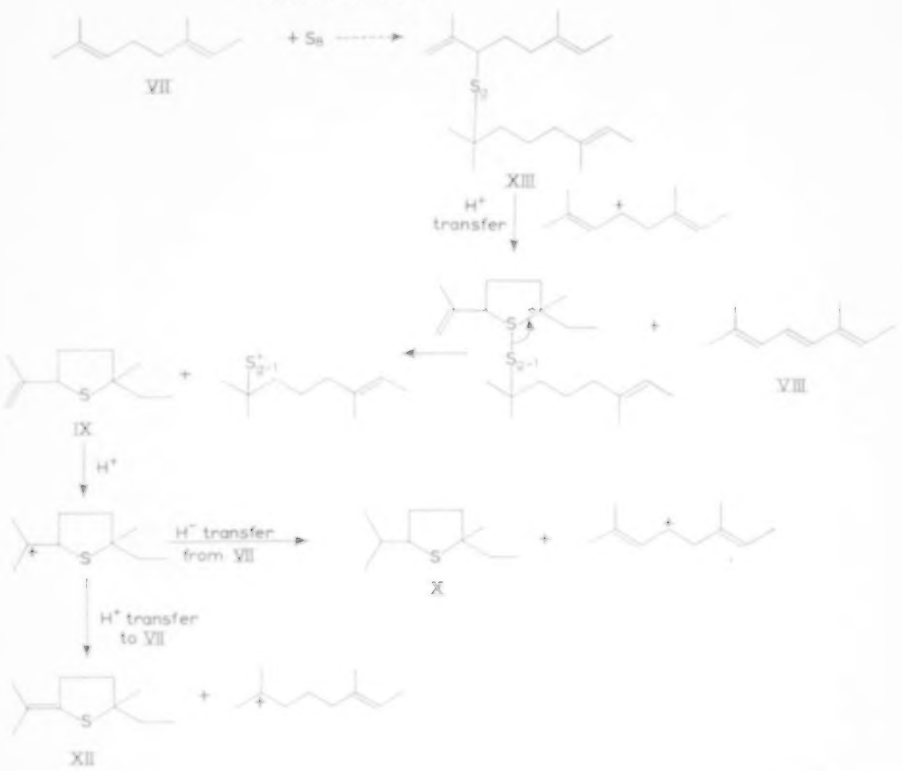


(7)

[5] G. W. Ross, *J. Chem. Soc.* 2856 (1958).
[6] L. Bateman, C. G. Moore and M. Porter, *J. Chem. Soc.* 2866 (1958).

The compounds (VIII)–(XII) result from subsequent reactions of initially formed polysulphides, as exemplified by the formation of (VIII), (IX), (X), and (XII) from the polysulphide (XIII) (Reaction scheme A).

Reaction scheme A

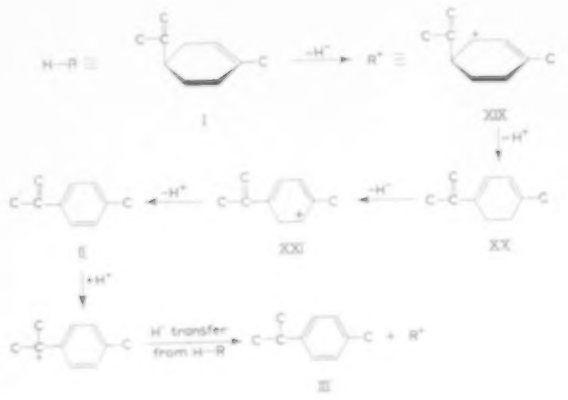


The above polar mechanism is now applied to explain the formation of (II)–(VI) from (+)-limonene (I), as expressed in Reaction scheme B in which reactions leading to the initial polysulphides (XIV)–(XVI) are restricted to the more reactive, trialkylethylenic, double bond of the (+)-limonene (cf. ref. 5). The two stereoisomeric polysulphides (XIV) and (XV) will predominate over the structural isomer (XVI), in keeping with the preferential formation of an *endo*- rather than *exo*-cyclic olefinic double bond in a six-membered ring system.[7] The cyclic sulphides (IV) and (VI) then result from protonation of the *iso*propenyl groups of (XV) followed by intramolecular heterolysis of an S—S bond by the *iso*propylium ion centre, as depicted in the scheme. The polysulphide (XIV) can act similarly as the precursor to (IV), but it cannot yield (VI) because of the *trans*- configuration of the *iso*propenyl and —S_a— substituents in the *cyclo*hexane ring. The cyclic sulphide (IV) is converted to (V) by an initial protonation reaction to give the carbonium ion (XVII) which then undergoes a stereospecific hydride ion (H^-) transfer from a suitable hydrogen donor, e.g. (I), to give (V). The stereospecificity of this H^- transfer will be assisted firstly, by interaction of the

[7] R. B. Turner and R. H. Garner, *J. Amer. Chem. Soc.* **80**, 1424 (1958).

carbonium ion centre in (XVII) with the sulphur atom of the thia*cyclo*pentane ring, leading to a preferred partial *trans*- configuration of the C_1—CH_3 and C_2—S— groups in the *cyclo*hexane ring of (XVII); and secondly, by the occurrence of greater steric hindrance when the above C_1—CH_3 and C_2—S— groups are in a *cis*- configuration, as revealed by molecular models. The formation of (V) from (IV), as required by the mechanism now proposed, is consistent with Weitkamp's finding[2] that the yield of

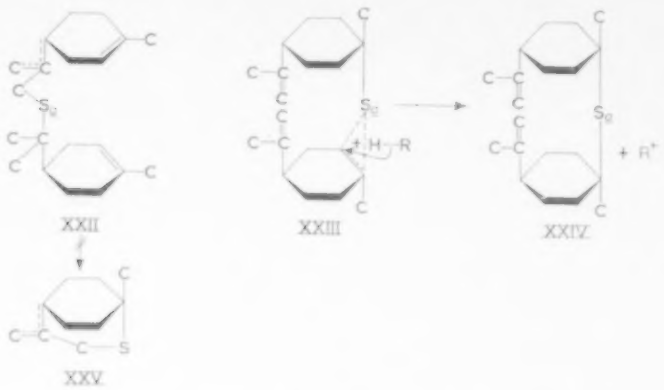
Reaction scheme B (continued)



(IV) decreases at the expense of (V) as the sulphuration reaction proceeds. The non-formation of the vinylicycyclic sulphide (XVIII), analogous to (XII) obtained from the acyclic 1:5-diene (VII), is explicable on the basis of the known instability of fused-bicyclic systems containing a bridgehead double bond (Bredt's Rule).[8] The fact that sulphuration of (+)-limonene yields optically active cyclic sulphides (+)-(IV) and (−)-(V) is also consistent with the proposed mechanism since the asymmetric centre at C_4 in the (+)-limonene is not destroyed in the reactions leading to (IV) and (V). It is also noteworthy that because of the stereochemical restrictions which must be imposed on the reaction intermediates which finally yield (IV) and (V) then additional centres of optical activity will be introduced into the latter two compounds, viz. at C_2 in (IV) and at C_1 and C_2 in (V). The hydrocarbons (II) and (III) are formed by a sequence of hydride ion- and proton-transfer processes analogous to those leading to the conjugated triene (VIII) from the 1:5-diene[6] (VII) (Reaction schemes A and B). The deprotonation of the mesomeric alkenyl cations (XIX) and (XXI) according to reaction (7) in preference to their alternative reaction with sulphur, reaction (6), is explicable on the basis of the energy gained from the formation of the conjugated hydrocarbons (XX) and (II), respectively.

The occurrence of initial sulphuration processes at the less reactive *iso*propenyl group of (+)-limonene, comparable to those detailed in Reaction scheme B, will lead to additional polysulphides, e.g. (XXII) in which the dotted lines represent alternative positions of the double bond. Further, if the intermediate cyclic persulphonium ions such as (XXIII) are stabilised by hydride ion transfer, reaction (4), as an alternative to deprotonation, reaction (3), then polysulphides such as (XXIV) will be formed. It is significant, however, that the polysulphides (XXII) and (XXIV) will not yield, by subsequent reactions analogous to those of Reaction scheme B, any alternative cyclic sulphides to those observed experimentally. Thus, both polysulphides will give (VI), but the substituted thia*cyclo*heptanes (XXV) theoretically derivable from (XXII) are unlikely to be formed because of unfavourable steric factors associated with the seven-membered ring and the bridgehead double bond.

[8] F. S. Fawcett, *Chem. Rev.* **47**, 219 (1950).



In conclusion, the experimental data of Weitkamp[1–3] provide critical support for the polar mechanism of olefinic sulphuration[5,6] which specifically explains the formation of the observed products (II)–(VI) from (+)-limonene, and of equal importance, does not predict any additional cyclic sulphide structures.

This work forms part of the programme of research undertaken by the Board of The British Rubber Producers' Research Association.

VOL. 6 1959

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BISCHLER–NAPIERALSKI REACTION—II*

SYNTHESIS OF SOME KETONIC *ISO*QUINOLINES

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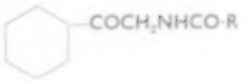
(*Received* 25 *August* 1958)

Abstract—Ethylene ketals of the type (I) cyclise in presence of phosphorus pentoxide in pyridine to give the ketal (II) which on hydrolysis yields 1-phenyl-6:7-dimethoxy-4-oxo-3:4-dihydro*iso*quinoline (III). 1-(4-oxo-*cyclo*hexyl)-6:7-dimethoxy-3:4-dihydro*iso*quinoline (VIII) and 2-oxo-3-methyl-9:10-dimethoxy-1:2:3:4:6:7-hexahydro-11bH-benzo[a]-quinolizine (XV) were also synthesised.

IN the first paper* of this series it was reported that substituted acyl-β-phenethylamides could be cyclised to the corresponding *iso*quinolines by treatment with phosphorus pentoxide in pyridine, and this has now been applied to compounds of the type



Buck first reported[1] that such compounds yielded 4-oxo*iso*quinoline derivative when treated with phosphoryl chloride, but later stated that the product really was an oxazole derivative.[2a,b] Cyclisation to *iso*quinoline derivatives can be achieved if the ketonic CO is protected by conversion to the ethylene ketal. Thus the ethylene ketal (I) from ω-benzamidoacetoveratrone is cyclised by phosphorus pentoxide in pyridine to 1-phenyl-4:4-ethylenedioxy-6:7 dimethoxy-3:4-dihydro*iso*quinoline (II) which on hydrolysis gives 1-phenyl-6:7-dimethoxy-4-oxo-3:4-dihydro*iso*quinoline (IIIa), or 1-phenyl-4-hydroxy-6:7-dimethoxy*iso*quinoline (IIIb), which on reduction by Huang-Minlon's method gives 1-phenyl-6:7-dimethoxy-3:4-dihydro*iso*quinoline (IV). In a similar manner 1-(4-oxo*cyclo*hexyl)-6:7-dimethoxy-3:4-dihydro*iso*quinoline (VIII) and 2-oxo-3-methyl-9:10-dimethoxy-1:2:3:4:6:7-hexahydro-11bH-benzo-[a]-quinolizine (XV) were synthesised. The latter is suitable for the synthesis of compounds related to emetine. The influence of various substituents in position 5 of the piperidone ring in (XII) on cyclisation is now being investigated.

EXPERIMENTAL

Ketal of ω-benzamidoacetoveratrone (I), ω-Benzamidoacetoveratrone[3] (1 g), ethylene glycol (0·3 g), *p*-toluenesulphonic acid (0·1 g) in benzene (50 cc) was refluxed for 3 hr in an apparatus provided with a Dean–Stark water separator 0·3 cc of water being collected. On cooling the benzene layer was washed with water, dried, and the solvent evaporated to a syrup (1·2 g) which solidified and crystallised from *n*-hexane in colourless needles (0·82 g, 75%) m.p. 109° (Found: C, 66·5; H, 5·9; N, 4·0; $C_{19}H_{21}O_5N$ requires: C, 66·5; H, 6·1; N, 4·1%).

* Part I. Nobuo Itoh and Shigehiko Sugasawa, *Tetrahedron* **1**, 45 (1957).
[1] J. S. Buck, *J. Amer. Chem. Soc.* **52**, 3610 (1930).
[2a] J. S. Buck, *J. Chem. Soc.* 740 (1933); [b] R. Robinson, *J. Chem. Soc.* 275 (1933).
[3] R. Robinson, *J. Chem. Soc.* **95**, 2167 (1909).

VOL.
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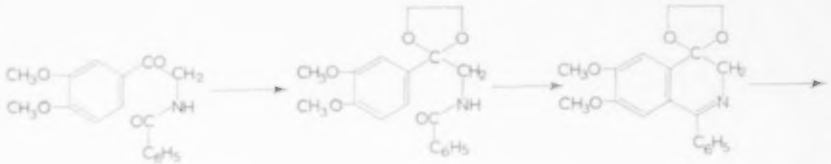
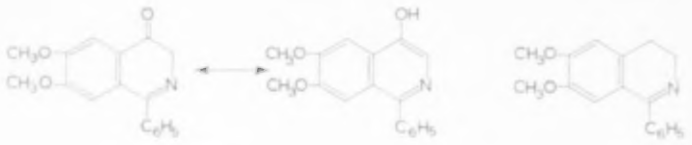
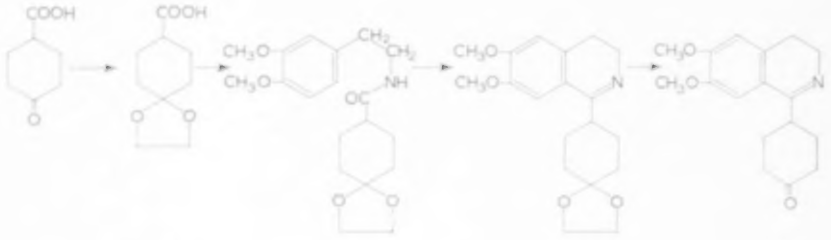


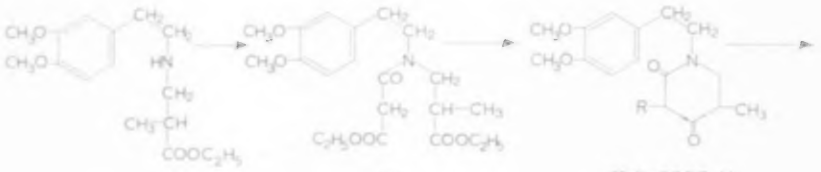
I II



III III′ IV

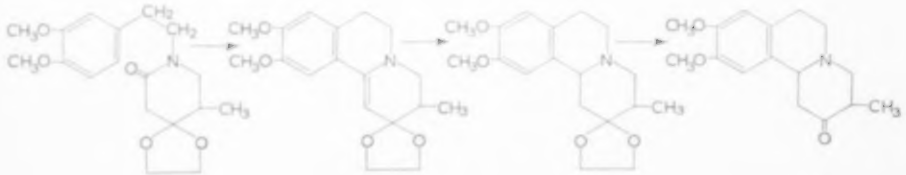


V VI VII VIII



IX

X: R = $COOC_2H_5$
XI: R = H



XII XIII XIV XV

1-*Phenyl*-4:4-*ethylenedioxy*-6:7-*dimethoxy*-3:4-*dihydroisoquinoline* (II). The ketal (I, 0·5 g) in pyridine (30 cc) was refluxed (oil-bath) and to the solution a mixture of phosphorus pentoxide (5 g) and purified sea sand (50 g) was added in four portions during 2 hr and boiling maintained for 6 hr. The dark brown pyridine layer was decanted, the residue washed with pyridine (3 × 10 cc) and the washings combined with the pyridine layer. Evaporation of the pyridine *in vacuo* left a reddish syrup, which was dissolved in benzene, filtered and the solvent removed leaving a reddish yellow syrup (0·38 g, 80%). The latter solidified and was crystallised from *n*-hexane in pale yellow needles m.p. 137° (Found: C, 70·7; H, 6·1; N, 4·3. $C_{19}H_{19}O_4N$ requires: C, 70·3; H, 5·9; N, 4·3%). The *picrate* formed yellow needles m.p. 162–163° from ethanol (Found: C, 54·0; H, 4·2; N, 10·3. $C_{25}H_{22}O_{11}N_4$ requires: C, 54·15; H, 4·0; N, 10·1%).

1-*Phenyl*-6:7-*dimethoxy*-4-*oxo*-3:4 *dihydroisoquinoline* (III). The hydrochloride of (III) was obtained as a colourless crystalline hygroscopic solid by heating (steam-bath) the ketal (II, 0·3 g) in HCl (5 cc, 10%) for 2 hr and subsequent evaporation. Treatment of the aqueous solution of the hydrochloride with potassium carbonate gave the base (III) which was dissolved in benzene dried, and the solvent evaporated leaving a yellow syrup (0·2 g, 79%) which rapidly darkened in air. The base was characterised as its 2:4-dinitrophenylhydrazone, red needles m.p. 201–203° (decomp.) from ethanol (Found: C, 60·1; H, 4·5; N, 15·0. $C_{23}H_{19}O_6N_5$ requires: C, 60·0; H, 4·1; N, 15·2%).

1-*Phenyl*-6:7-*dimethoxy*-3:4-*dihydroisoquinoline* (IV). The base (III, 0·3 g) was reduced by treatment with KOH (0·2 g) hydrazine hydrate (0·2 g) and ethylene glycol (0·5 g) and heating in an oil-bath for 2 hr at 140° and then at 170° for 2 hr. The red product was extracted with benzene and the solution washed, dried and the solvent removed leaving a viscous mass (70 mg) which partially solidified. It was obtained as colourless prisms from *n*-hexane, m.p. 121° and was identified with an authentic specimen. The yield was 42 mg (14%).

4:4-*Ethylenedioxy*cyclo*hexane carboxylic acid* (V). This was prepared by heating a mixture of ethyl 4-oxo-*cyclo*hexanecarboxylate[4] (6·1 g), ethylene glycol (2·5 g), *p*-toluenesulphonic acid (0·1 g) in benzene (50 cc) for 4 hr, using the apparatus previously mentioned. After collecting 1 cc of water, an oil b.p. 140–145°/15 mm (6 g, 83%) was obtained, and this was hydrolysed by refluxing with NaOHaq. and methanol. The acid (V) was obtained from the sodium salt by neutralisation with dilute HCl with cooling. The acid was extracted with ether and obtained as a colourless oil (2·6 g, 50%) b.p. 131–136°/2 mm. A small portion of this oil treated with dilute HCl gave the corresponding ketonic acid m.p. 67–68° which was not depressed on mixing with an authentic specimen.[4]

4′:4′*Ethylenedioxy*-cyclo*hexane-carbox*-(3:4-*dimethoxyphenethyl*)-*amide* (VI). The acid (V, 2·6 g) in ether was converted to the chloride with thionyl chloride (1·2 g). The solvent and excess of thionyl chloride were removed *in vacuo* and the reddish residue (2·5 g) was dissolved in benzene, and the solution treated with 3:4-dimethoxyphenethylamine (1 g) in the presence of potassium carbonate (1·5 g). The amide (VI) was obtained as a yellow gum which solidified (1·5 g) and crystallised from a mixture of benzene and *n*-hexane as colourless needles (0·8 g) m.p. 109–110° (Found: C, 65·7; H, 7·4; N, 3·9. $C_{19}H_{27}O_5N$ requires: C, 65·3; H, 7·7; N, 4·0%). On refluxing a

[4] R. H. Martin and R. Robinson, *J. Chem. Soc.* 491 (1943).

solution of the ketal amide (0·2 g) in ethanol (10 cc) with HCl (2 cc, 2%) for 2 hr, the *ketonic amide* was obtained in quantitative yield as colourless needles m.p. 143–145° from *n*-hexane (Found: C, 66·6; H, 7·4; N, 4·3. $C_{17}H_{23}O_4N$ requires: C, 66·9; H, 7·5; N, 4·6%). The 2:4-*dinitrophenylhydrazone* was obtained as orange needles m.p. 206–207° (decomp.) from ethanol (Found: C, 56·7; H, 5·2; N, 14·2. $C_{23}H_{27}O_7N_5$ requires: C, 56·9; H, 5·5; N, 14·4%).

1-(4′:4′-*Ethylenedioxy*cyclo*hexyl*)-6:7-*dimethoxy*-3:4-*dihydro*isoquinoline (VII). The amide (VI, 0·5 g) in pyridine (30 cc) was cyclised with phosphorus pentoxide (5 g) as described above. The reddish syrup (0·5 g) was dissolved in benzene, washed and dried and the solvent evaporated leaving a reddish syrup which could not be crystallised. It was converted to the *picrate* which crystallised as yellow needles m.p. 103–104° from ethanol (Found: C, 52·3; H, 5·4; N, 9·5. $C_{25}H_{28}O_{11}N_4$, $\frac{1}{2}H_2O$ requires: C, 52·7; H, 5·2; N, 9·8%). The yield of picrate was good (75%).

1-(4′-*oxo*-cyclo*hexyl*)-6:7-*dimethoxy*-3:4-*dihydroisoquinoline* (VIII). A solution of (VII, 0·3 g) in HCl (5 cc, 10%) was heated (steam-bath) for 2 hr. On cooling, the solution was shaken with benzene to remove undissolved matter and treated with charcoal, filtered and the filtrate treated with potassium carbonate. The base was extracted with benzene, dried and the solvent evaporated leaving a yellow syrup (0·24 g) which darkened in the air. The *picrate*, yellow needles m.p. 161° (decomp.) from ethanol (Found: C, 53·3; H, 4·8; N, 10·5. $C_{23}H_{24}O_{10}N_4$ requires: C, 53·5; H, 4·65; N, 10·85%).

The 2:4-*dinitrophenylhydrazone*, yellow needles m.p. 179–180° (decomp.) from ethanol (Found: C, 59·5; H, 5·6; N, 15·2. $C_{23}H_{25}O_6N_5$ requires: C, 59·1; H, 5·35; N, 14·9%).

1-(3′:4′-*Dimethoxyphenethyl*)-4-*oxo*-5-*methyl*-*piperid*-2-*one* (XI). To a solution of ethyl N-(3:4-dimethoxyphenethyl)-N(2′-ethoxycarbonylpropyl)-malonamidate[5] (IX, 16 g) in xylene (50 cc), sodium dust (0·8 g) was added and the mixture refluxed (oil-bath) for 3 hr when the evolution of H ceased and the sodium compound of the ketonic ester (X) separated. After cooling, the xylene layer was decanted and the sodium compound was dissolved in ice cold water acidified with dilute HCl, and the ketonic ester extracted with benzene yielding (X, 14·2 g). It gave a reddish ferric chloride reaction. The crude ester was subjected to ketonic fission by dissolving in acetic acid (10%) and refluxing for 3 hr when the evolution of CO_2 ceased. The solution was neutralised with sodium bicarbonate solution, extracted with benzene and the solution repeatedly extracted with sodium hydroxide solution (10%). The ketopiperidone was obtained from the aklaline solution by acidifying with HCl and extracting with benzene, dried and the solvent evaporated leaving a syrup (7·2 g, 64%) which solidified, and crystallised from benzene and *n*-hexane in colourless needles m.p. 94–95° (Found: C, 66·25; H, 7·1; N, 4·6. $C_{16}H_{21}O_4N$ requires: C, 65·95; H, 7·3; N, 4·8%). (XI) gave no ferric chloride reaction. Infra-red spectrum Nujol 1655 cm^{-1} (lactam C=O), Nujol 1722 cm^{-1} (ketone C=O). The 2:4-*dinitrophenyl hydrazone* formed yellowish red needles m.p. 202–203° (decomp.) from ethanol (Found: C, 55·9; H, 5·6; N, 15·5. $C_{22}H_{25}O_7N_5$ requires: C, 56·05; H, 5·3; N, 14·9%).

2:2-*Ethylenedioxy*-3-*methyl*-9:10-*dimethoxy*-3:4:6:7-*tetrahydro*-2H-*benzo*[a]*quinolizine* (XIII). The ketone (XI) was converted to ketal (XII) as described above, and

[5] K. Mizukami, *Chem. Pharm. Bull. Japan* **6**, 312 (1958).

obtained as a yellow syrup (85%) which was free from the ketone (XI). Infra-red spectrum (capillary 1645 cm^{-1}, lactam C=O, no band in the ketonic region). The crude ketal (1 g) was cyclised with phosphorus pentoxide (5 g) in pyridine with sea sand for 6 hr. The product, obtained as a yellow jelly (0·8 g) was dissolved in acetic acid (5%), filtered through a wet filter and the base liberated by addition of potassium carbonate and extracted with benzene which on evaporation left a syrup (0·3 g, 38%). The *picrate* crystallised in yellow needles from ethanol m.p. 200° (effervescence) (Found: C, 49·6; H 4·6; N 10·1. $C_{24}H_{26}O_{11}N_4$, 1·5 H_2O requires: C, 50·3; H, 5·1; N, 9·8%. $C_{24}H_{26}O_{11}N_4$, $2H_2O$ requires C, 49·5; H, 5·0; N, 9·6%).

2:2-*Ethylenedioxy*-3-*methyl*-9:10-*dimethoxy*-1:2:3:4:6:7-*hexahydro*-11bH-*benzo*[a]*quinolizine* (XIV). The reduction of (XIII) (0·2 g) was carried out in presence of Raney nickel, 1 molar equivalent of hydrogen being absorbed in 2 hr. The product was obtained as a syrup which did not crystallise. The *picrate* was obtained as yellow needles from ethanol m.p. 203–204° (decomp.) (Found: C, 52·8; H, 5·3; N, 10·2. $C_{24}H_{28}O_{11}N_4$ requires: C, 52·55; H, 5·1; N, 10·2%).

2-*Oxo*-3-*methyl*-9:10-*dimethoxy*-1:2:3:4:6:7-*hexahydro*-11bH-*benzo*[a]*quinolizine* (XV). The ketal (XIV) is readily hydrolysed with HCl (5%) by heating (steam-bath) for 2 hr. On working up the product as described above (XV) was obtained as a yellow jelly which solidified and crystallised from *n*-hexane in colourless needles m.p. 139° and was identified by comparison with an authentic specimen of (XV) synthesised by Mizukami by a different method (Found: C, 67·55; H, 7·95; N, 5·1. Calc. for $C_{16}H_{21}O_3N$, $0{\cdot}5H_2O$, C, 67·6; H, 7·7; N, 4·9%). The *picrate* crystallises in yellow needles from ethanol m.p. 197–198° (decomp.) (Found: C, 52·2; H, 5·1; N, 11·1 $C_{22}H_{24}O_{10}N_4$ requires: C, 52·4; H, 4·8; N, 11·1%). The *hydrochloride* of the base crystallises as colourless plates from ethanol m.p. 198–199° (decomp.) (Found: C, 58·2; H, 7·85; N, 4·4. $C_{16}H_{22}O_3NCl$, H_2O requires: C, 58·3; H, 7·3; N, 4·2%). The 2:4-*dinitrophenylhydrazone hydrogen sulphate* crystallises in yellow prisms from ethanol m.p. 173–174° (Found: C, 47·8; H, 5·3; N, 12·9. $C_{22}H_{25}O_6N_5$, H_2SO_4 requires: C, 47·7; H, 4·9; N, 12·7%).

Acknowledgement—The authors are grateful for a generous supply of pyridine from Mr. Masuo Nakamura, Vice-President of Yawata Chemical Industries Ltd.

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A STUDY OF LEUCOANTHOCYANIDINS OF PLANTS—II[1]

(+)LEUCOCYANIDIN FROM THE GUM OF *BUTEA FRONDOSA*

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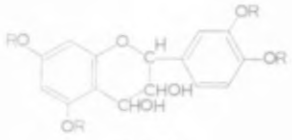
(*Received* 9 *September* 1958)

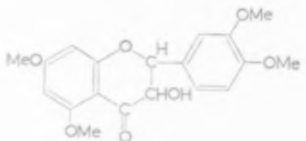
VOL. 6 1959

Abstract—A (+)leucocyanidin has been isolated from the gum of *Butea frondosa*, its acetate and methyl ether prepared and studied. The leucocyanidin is 5:7:3′:4′-tetrahydroxyflavan-3:4-diol. The methyl ether and the acetate have also been prepared by borohydride reduction of taxifolin tetramethyl ether and taxifolin respectively.

LEUCOCYANIDIN has now been extracted from the gum of *Butea frondosa* which was earlier used as a good source for the preparation of cyanidin chloride.[2] Leucocyanidin ($C_{15}H_{14}O_7$) is phenolic in character, dextrorotatory and gives all the reactions characteristic of a leucoanthocyanidin. With diazomethane it gives a tetramethyl ether which yields a diacetate showing the presence of two alcoholic groups. Oxidation of the tetramethyl ether with potassium permanganate yields veratric acid. Leucocyanidin reduces periodic acid indicating the presence of a diol grouping, and its infra-red spectrum has no C=O bond. Hence leucocyanidin of *Butea* gum should be represented as 5:7:3′:4′-tetrahydroxyflavan-3:4-diol (I).



I, R=H
II, R=Me



II

In the present investigation taxifolin tetramethyl ether (II) has been reduced by sodium borohydride (compare)[3] giving a mixture of two isomeric leucocyanidin tetramethyl ethers (III) m.p. 172° and 198° respectively. Both isomers give anthocyanidin chloride on boiling with alcoholic HCl, and do not give a coloration with ferric chloride. The higher melting isomer agrees with the tetramethyl ether of natural leucocyanidin and the infra-red spectra have similar bands in the region 2–12 μ. It is suggested that the higher melting isomer is the racemic form of the natural compound and the lower melting one is another of the possible racemic forms. It was not possible to obtain leucocyanidin in a pure condition by reduction of taxifolin; the product was converted into leucocyanidin hexa-acetate, which was also obtained from leucocyanidin by acetylation. Taxifolin penta-acetate has yielded a product which does not agree with the acetate of the natural compound.

[1] A. K. Ganguly, T. R. Seshadri and P. Subramanian, *Tetrahedron* **3**, 225 (1958).
[2] G. M. Robinson, *J. Chem. Soc.* 1157 (1937).
[3] T. Swain, *Chem. & Ind.* 1144 (1954).

EXPERIMENTAL

Isolation of leucocyanidin. The *Butea* gum was obtained from the Central Lac Research Institute, Ranchi. The powdered gum (600 g) was extracted successively with light petroleum and ether at room temp to remove wax. A small quantity of a pale yellow solid was obtained from the ether extract. It did not give any colour with magnesium or zinc and hydrochloric acid. In the Liebermann-Burchard reaction it gave a red colour changing to violet, green and finally to brown. The quantity of the substance was too small for further investigation.

The residual gum was extracted repeatedly with cold acetone, and the combined extracts were distilled under reduced pressure to remove the solvent almost completely. The viscous red liquid residue was repeatedly extracted with ethyl acetate, and the extract dried over anhydrous magnesium sulphate and then concentrated under reduced pressure. By gradual addition of light petroleum, coloured impurities were precipitated first and then with further addition of light petroleum, the leucocyanidin was obtained as a colourless solid. Repeated purification from a mixture of ethyl acetate and light petroleum yielded a crystalline powder (15 g). It darkened at 280° and did not melt at 355°. (Found: C, 55·2; H, 5·1; $C_{15}H_{14}O_7$, H_2O requires: C, 55·5; H, 4·9%). The product was insoluble in ether, chloroform and petroleum ether but was soluble in water, alcohol and acetone. With alcoholic HCl it developed a red colour in the cold which deepened on heating, and with alcoholic ferric chloride gave a green colour changing to blue on standing. In the ultra-violet region the alcoholic solution of the leucocyanidin had an absorption maximum at 285 mμ. The ethanolic solution was dextrorotatory, but definite values could not be obtained because the solution of the leucocyanidin developed colour rapidly.

Conversion into cyanidin chloride was effected following the procedure described for leucodelphinidin;[1] yield 10%. The anthocyanidin chloride gave a positive ferric reaction and a rose red colour when extracted with cyanidin reagent; R_f (circular) using phenol-water lower layer at 29°, 0·72. The ethanolic HCl solution had an absorption maximum at 544 mμ. Treatment of leucocyanidin (0·2 g) with acetic anhydride (4 cc) and dry pyridine (1 cc) in the cold for 48 hr yielded a colourless *acetate* (0·1 g) which crystallised from a mixture of ethyl acetate and light petroleum as colourless irregular prisms, m.p. 270° (d) sintering at 264°. (Found: C, 58·8; H, 5·0; $C_{27}H_{26}O_{13}$ requires: C, 58·1; H, 4·7%). It did not give any colour with alcoholic ferric chloride and with boiling alcoholic HCl it developed a red colour. The infra-red spectrum of the above *acetate* had the following main bands in microns: 5·70(s), 6·25(s), 6·68(m), 7·25(s), 8·25(w), 8·50(w). The leucoanthocyanidin (2 g) was methylated in methanol solution using diazomethane in the cold. The colourless *methyl ether* (1·5 g) crystallised from methanol as prisms, m.p. 198–200° sintering at 190°, $[\alpha]_D^{32}$ +125·2° (*c*, 0·2 in ethanol). (Found: C, 63·0; H, 6·1; $C_{19}H_{22}O_7$ requires: C, 63·0; H, 6·1%). It was insoluble in aqueous alkali and gave no ferric colour. The infra-red spectrum of leucocyanidin *tetramethyl ether* had the following main bands in microns: 2·95(s), 3·50(s), 6·27(s), 6·56(s), 7·90(m), 8·30(m), 8·70(w), 9·73(m). A colourless *acetate of the ether* was obtained using acetic anhydride and pyridine in the cold. It crystallised from a mixture of ethyl acetate and light petroleum as circular tablets m.p. 215–218°. (Found: C, 62·0; H, 5·5; $C_{23}H_{24}O_9$ requires: C, 61·9; H, 5·8%). Potassium permanganate was added to a boiling acetone solution of the *methyl ether* during the course of 4 hr. It was worked up as described previously.[1] The purified acid melted at 180–181°, alone or mixed with an authentic sample of veratric acid; R_f (circular) using butanol saturated with ammonia as solvent and bromophenol blue as developer at 30°C, 0·44; authentic sample of veratric acid under the same conditions gave R_f 0·44.

Periodic acid oxidation of leucocyanidin. An ethanolic solution of leucocyanidin (0·0066 M 1 cc) was allowed to react with periodic acid solution (0·0142 M 5 cc) for 24 hr at room temp. The reaction mixture was treated with excess potassium iodide solution and the liberated iodine titrated against standard arsenious oxide solution. For each mole of leucocyanidin 1·8 moles of periodic acid were consumed.

Reduction of taxifolin tetramethyl ether. To an ice cold solution of taxifolin tetramethyl ether (0·2 g) in methanol, sodium borohydride (60 mg) was added and after allowing the mixture to stand at room temp for 48 hr it was acidified with acetic acid and the solvent removed almost completely under reduced pressure and the residue kept in the vacuum desiccator over potassium hydroxide. The resulting colourless solid was washed with a little water, dried and crystallised from methanol; two fractions were obtained. The first (80 mg) on recrystallisation from ethanol yielded colourless needles, m.p. 171–172°. (Found: C, 62·8; H, 6·4; $C_{19}H_{22}O_7$ requires: C, 63·0; H, 6·1%); the

second (60 mg) gave colourless rectangular rods, m.p. 198° with previous sintering at 192°. (Found: C, 62·7; H, 5·9; $C_{19}H_{22}O_7$ requires: C, 63·0; H, 6·1%). The mixed m.ps. of both fractions with taxifolin tetramethyl ether were depressed. The second fraction did not depress the m.p. of the methyl ether of leucocyanidin obtained from butea gum.

Reduction of taxifolin. Taxifolin (0·15 g) was reduced in methanol solution using sodium borohydride (50 mg, excess) in the cold. It was worked up as above and the crude reduction product was acetylated using acetic anhydride and pyridine at room temp. The colourless acetate (0·1 g) crystallised from a mixture of ethyl acetate and light petroleum as clusters of small prisms m.p. 270° (d) with previous sintering at 263°, unaffected by admixture with natural leucocyanidin acetate (Found: C, 57·6; H, 4·7; $C_{27}H_{26}O_{13}$ requires: C, 58·1; H, 4·7%).

Reduction of taxifolin acetate. It was carried out using the acetate (0·2 g) in methanol solution and sodium borohydride (50 mg, excess). The product was acetylated using acetic anhydride and pyridine in the cold. The colourless hexa-acetate (0·1 g) was purified from a mixture of ethyl acetate and light petroleum, m.p. 204° with previous sintering at 190° (Found: C, 57·8; H, 5·0; $C_{27}H_{26}O_{13}$ requires: C, 58·1; H, 4·7%). It did not give a colour with alcoholic ferric chloride.

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MECHANISM OF REACTION OF METHYLENE WITH THE CARBON–HYDROGEN BOND

EVIDENCE FOR DIRECT INSERTION

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Abstract—The photolysis of diazomethane in 2-methylpropene-1-^{14}C leads predominantly to 2-methylbut-1-ene-1-^{14}C whether the reaction be run in the liquid or gas-phase. This result is the first unequivocal evidence in support of mechanisms involving direct insertion of methylene into the carbon–hydrogen bond.

In the gas-phase, recovered 2-methylpropene shows a small amount of mixing of radioactivity while the 2-methylbutene-1 shows as much as 8 per cent. The intervention of free radicals as a side-reaction is indicated.

MEERWEIN and his coworkers[1,2] discovered that the photochemical decomposition of diazomethane in organic solvents can lead to the formation of methyl groups. Superficially the reaction involves the insertion of methylene into the carbon–hydrogen bond. However, the presence of oxygen in their examples makes it conceivable[3] that an intermediate "ylid" may have been involved.† Examples of the reaction of the saturated carbon–hydrogen bond of aliphatic hydrocarbons with diazomethane[4] and methyl diazoacetate,[5] brought to light later, brook no question of the formation of "ylids" or other prior complexes.‡

The mechanism of the reaction is most simply conceived as a direct insertion and has been represented accordingly (Chart 1, A).[5,8,9] The possibility of free radical mechanisms is also reasonable. A chain mechanism (Chart 1, B–B″) receives its clearest support in the fine work of Urry and Eiszner[10] and is given general formulation in Chart 1. A non-chain scheme (Chart 1, B–B′) has been constructed by Frey and

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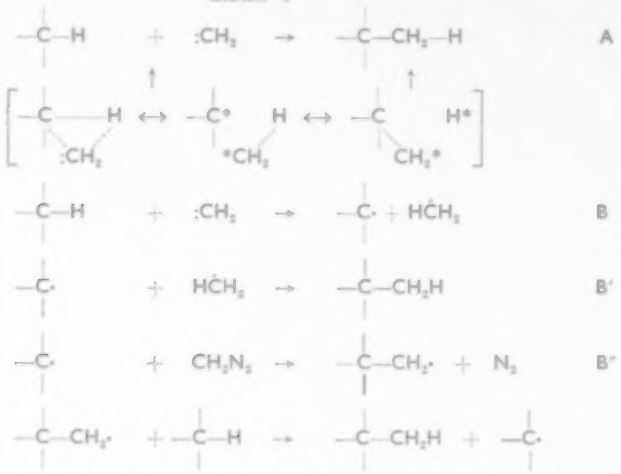
† In the reaction of tetrahydrofuran with diazomethane, the absence of tetrahydropyran (more than 0·05% could have been detected) leaves one with no compelling reason to invoke an "ylid" (W. von E. Doering, L. H. Knox and M. Jones, *J. Org. Chem.* In press).

‡ The question of whether methylene reacts directly with methane to give ethane is still unresolved.[6,7,8]

[1] H. Meerwein, H. Rathjen and H. Werner, *Ber.* **75**, 1610 (1942).
[2] H. Meerwein, H. Disselnkoetter, F. Rappen, H. v. Rintelen and H. van de Vlood, *Liebigs Ann.* **604**, 151 (1957).
[3] R. Huisgen, *Angew. Chem.* **67**, 439 (1955).
[4] W. von E. Doering, R. G. Buttery, R. G. Laughlin and N. Chaudhuri, *J. Amer. Chem. Soc.* **78**, 3224 (1956).
[5] W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.* **78**, 4947 (1956).
[6] F. Grard and M. Vanpee, *Bull. Soc. Chim. Belg.* **60**, 208 (1951).
[7] C. Rosenblum, *J. Amer. Chem. Soc.* **63**, 3322 (1941).
[8] J. Chanmugam and M. Burton, *J. Amer. Chem. Soc.* **78**, 509 (1956).
[9] J. H. Knox and A. F. Trotman-Dickenson, *Chem. & Ind.* 268 (1957). These workers invoke a similar mechanism for the reaction of CH_2 with H_2.
[10] W. H. Urry and J. R. Eiszner, *J. Amer. Chem. Soc.* **73**, 2977 (1951); **74**, 5822 (1952).

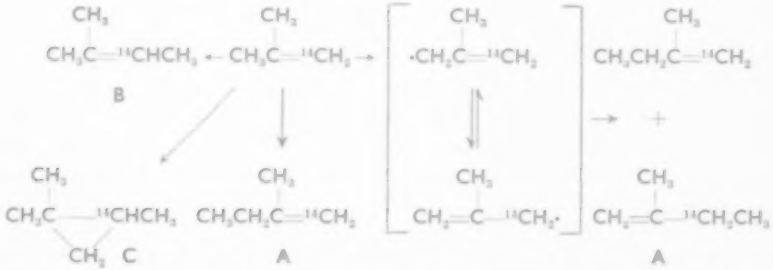
Kistiakowsky[11] as an explanation for the production of ethane in the reaction of methylene with propane and butane.

CHART 1



Distinction between the radical mechanisms and direct insertion—the first involving intermediate fragmentation; the other not—is a step in understanding the mechanism of the reactions of methylene. The distinction can be made with a molecule capable of giving a radical, which, if free, could then react further at a site other than the one involved in its initial formation. Such a molecule cannot consist only of saturated, alkyl carbon–hydrogen bonds and, most simply, is an olefin, whereupon, to be precise, the investigation becomes a study of the allyl carbon–hydrogen bond. 2-Methylpropene-1-^{14}C was the specific molecule chosen. Here, the product of interest, 2-methylbutene-1 (Chart 2, A), is expected to show radioactivity in the 1-position alone, if the mechanism be concerted, and activity in the 3-position as well, if a step-wise process with free intermediates or their equivalent be involved.

CHART 2



2-Methylpropene-1-^{14}C seemed advantageous from several points of view. Its vapor-pressure makes it suitable for study in both the liquid and gas-phase, a consideration of importance in view of the significant differences uncovered by Frey and Kistiakowsky[11] and by Knox and Trotman-Dickenson.[9] The products—2-methylbutene-1 (A), 2-methylbutene-2 (B) and 1:1-dimethyl*cyclo*propane (C)—are

[11] H. M. Frey and G. B. Kistiakowsky, *J. Amer. Chem. Soc.* **79**, 6373 (1957).

of sufficiently high volatility to be separable by gas–liquid-partition-chromatography (g.l.p.c.). The three main reaction products can be separated on a 4 meter column of dioctyl phthalate from each other and from the remaining starting material, from all the decomposition products of diazomethane and from small amounts of C_6-compounds formed as by-products. The products are identified by comparing their infrared spectra with those of authentic samples. Further purification of the 2-methylbutene-1 is effected on a silicone column and affords material having an infrared spectrum completely indistinguishable from that of the authentic material. The ratio of 2-methylbutene-2 to 2-methylbutene-1 to 1:1-dimethyl*cyclo*propane in the liquid phase reaction was roughly 1 : 2·5 : 8 whereas in the gas-phase the ratio of the latter two products was 1 : 3·5.

Labeled 2-methylpropene-1-^{14}C has been synthesized by Reeve and Chambers[12] from 2-methylpropan-1-ol-1-^{14}C by treatment with phosphorus and iodine followed by elimination with potassium hydroxide. Since there was no indication of the accuracy of their analyses and some reason to expect the formation of *t*-butyl iodide in the transformation of the carbinol, we did not rely on this method. Labeled 2-methylpropene has also been reported by Andrianova and Andreev[13] as the product of dehydrating 2-methylpropan-1-ol-1-^{14}C over alumina at 415°. In view of the experiences of Fries and Calvin[14] in dehydrating propan-1-ol-1-^{14}C under similar conditions and the lack of explicit indication of the distribution of radioactivity in the resulting 2-methylpropene, this method was also rejected.

In this work the general olefin synthesis of Wittig[15] was applied to acetone. Labeled triphenylphosphinemethylene was prepared from radioactive methyl iodide and triphenylphosphine followed by treatment of the phosphonium iodide with phenyl lithium. (The use of butyl lithium led to difficultly separable butane as a by-product.) The reaction of acetone and the "ylid" proceeded smoothly and led to 2-methylpropene-1-^{14}C which could be isolated in a pure state by g.l.p.c. By a method to be described in detail below, it was found to have all radioactivity at C_1 and no significant activity in the remainder (Table 1). This method is quite convenient for the preparation of small quantities of material, makes efficient use of radioactive methyl iodide (60–70 per cent of theory) and is therefore suitable for the preparation of material of high specific activity.

In this synthesis one has incontrovertible support for the hypothesis that the elimination in the final stage of the Wittig reaction proceeds without rearrangement. Although the gross structural outcome of the Wittig reaction has been abundantly clear in the numerous examples in the literature, it seems helpful to have rearrangement eliminated even as a minor side-reaction.

Radioactivity was determined by the new procedure of Wolfgang and Rowland.[16] The elegance, convenience and reliability of this method for organic chemical problems involving volatile materials cannot be overemphasized. By coupling a g.l.p.c. system in series with an integrating proportional flow counter Wolfgang and Rowland combined the powerful separating qualities of gas–liquid partition–chromatography

[12] W. Reeve and D. H. Chambers, *J. Amer. Chem. Soc.* **73**, 4499 (1951).
[13] T. I. Andrianova and E. A. Andreev, *Dokl. Akad. Nauk SSSR* **87**, 45 (1952); *Chem. Abstr.* **48**, 106c (1954); *Chem. Zentr.* 7515 (1953).
[14] B. A. Fries and M. Calvin, *J. Amer. Chem. Soc.* **70**, 2235 (1948).
[15] G. Wittig and U. Schoellkopf, *Ber.* **87**, 1318 (1954).
[16] R. Wolfgang and F. S. Rowland, *Analyt. Chem.* **30**, 903 (1958).

TABLE 1. DISTRIBUTION OF RADIOACTIVITY IN 2-METHYLPROPENE (C_4) AND 2-METHYLBUTENE-1 (C_5)

	αC_1OH[a,b]	αC_3OH	αC_4OH
Starting C_4	40,050	0[c]	
Rec. C_4 liquid dil	5,280	37	
Rec. C_4 liquid conc	45,530	906	
Rec. C_5 liquid conc	20,060		170
Rec. C_4 gas	13,525	420	
Rec. C_5 gas (400 mm)	10,435		892

[a] Activities, α, are in disintegrations per second per millimole calculated from the formula: $\alpha = N(F_{He} + F_{Me})/60\,V_m$. N is the total number of counts recorded from a given sample peak flowing through the counter; F_{He} and F_{Me} are flow rates in ml per minute of helium and methane, V is the volume of the counter and m is the quantity of substance in millimoles.

[b] Subscripts C_1OH, C_3OH and C_4OH denote methanol, propanol-2 and butanol-2 obtained by the ozonolysis-reduction of the olefin.

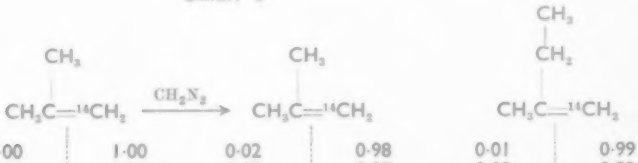
[c] The background is in the order of magnitude of 40 to 60 counts per minute. A minimum of 20 cpm can be observed with assurance (corresponding to 1·4 dps for a flow rate of 27 ml/min of helium and methane respectively).

with rapid, reliable counting. The method avoids tedious preliminary separation and the preparation of solid derivatives and is thus extraordinarily well suited to work with small quantities of material. The method has permitted all phases of this problem to be carried out on the small scale necessary to profit conveniently from the advantage of the powerful g.l.p.c. method.

Distribution of radioactivity in starting material and product was determined by ozonizing the olefin in pentane, reducing the ozonide with lithium aluminum hydride and passing the resulting solution of alcohols into the Wolfgang train without any prior separation.

The irradiation in the liquid phase was carried out in the usual way with sunlamps as the source of ultraviolet light but at considerably higher concentrations than those required for optimum yield of products. The gas-phase irradiations were carried out at a total pressure of 400 mm. The results of irradiation in the liquid phase and in the gas phase are shown in Chart 3 and in somewhat greater detail in Table 1. In both cases it is clear that the distribution of radioactivity in the 2-methylbutene-1 is far from the 0·50–0·50 values predicted on the basis of a free radical intermediate. These results constitute the first demonstration that methylene can react with a carbon–hydrogen bond by direct insertion (Chart 2, A). The results in the gas-phase are the more striking because in that phase there is no solvent cage to force the return of incipient free radicals (Chart 2, B-B′).

CHART 3



Liquid phase	0·00	1·00	0·02	0·98	0·01	0·99
Gas phase	0·00	1·00	0·03	0·97	0·08	0·92

The gas-phase reaction is, however, not clean cut. Redistribution in the 2-methylbutene-1 occurs to the extent of 8 per cent. Its seems unlikely for a number of reasons

that this mixing occurs by the decomposition of initially formed "hot" 1:1-dimethyl-*cyclo*propane. 3-Methyl-butene-1 would be expected among the products of this decomposition, but, in fact, cannot be detected (less than 0·05 per cent). The total pressure (400 mm) of the reactions is considerably higher than the range in which decomposition of "hot" 1:2-dimethyl*cyclo*propanes occurs to an appreciable extent.* It is much more reasonable to ascribe the mixing to the intervention of free radicals. It is significant that mixing occurs to an appreciable extent in the 2-methylpropene-1 recovered from the gas-phase reaction. A similar rearrangement is to be seen in the observation that one of the minor products of the reaction of *cis*-butene with diazomethane is butene-1.[17] These reactions are almost certainly brought about by free radicals. A chain process (Chart 2, B-B″) is a simple way of accommodating the observations.

EXPERIMENTAL

Photochemical decomposition of diazomethane and 2-methylpropene

In all experiments diazomethane is prepared in the following way: 10 g of nitrosomethylurea[18] is added in small amounts with vigorous stirring during 15 min to 30 ml of 50% potassium hydroxide and 75 ml of distilled decalin at 0°. The decalin-diazomethane layer is decanted and dried over potassium hydroxide. Such a solution can be kept at −70° without decomposition. Out of such a solution the diazomethane is transferred into the reaction vessels either by means of a stream of nitrogen or a vacuum system. In order to obtain products of sufficiently high specific activity the standard conditions for the reaction between diazomethane and hydrocarbons involving very dilute solutions had to be replaced by much higher concentrations of diazomethane. An illustrative procedure is given below.

Diazomethane from 10 g of nitrosomethylurea is blown by a slow stream of nitrogen into 500 mg of condensed 2-methylpropene. The reaction vessel is designed so that the Dry Ice condenser extends just to the surface of the liquid in order to minimize reaction in the gas-phase. The reaction vessel is cooled by flowing water and irradiated with 2 Westinghouse sunlamps (Type R S). After 6 hr all the diazomethane from the decalin solution has been transferred and irradiation is continued for one additional hour. The slightly yellow reaction products are separated on a 4 m column of dioctylphthalate on firebrick at 20° ("A"-column). Besides ca. 85% of recovered 2-methylpropene, decomposition products of diazomethane and small amounts of higher boiling C_6-products, three main reaction products are isolated: 1:1-dimethyl*cyclo*propane, 2-methylbutene-1 and 2-methylbutene-2. The ratio of the yields of these products roughly estimated from their peak heights is 8 : 2·5 : 1. They are finally purified on a 10 ft silicone column ("C"-column at 20° and identified by comparison of their g.l.p.c. retention times and of their infrared spectra with those of authentic samples (1:1-dimethyl*cyclo*propane was synthesized by the procedure given by Shortridge *et al.*[19]).

2-*Methylpropene*-1-^{14}C. Methyliodide-^{14}C (180 mg of methyliodide-^{14}C of 50 microcuries activity, obtained from New England Nuclear Corp., Boston, Mass., and 2·16 g of inactive methyliodide, a total of 16·5 mmole) and triphenylphosphine, (4·74 g, 18·1 mmoles) are mixed in 25 ml of anhydrous benzene at 0° in a 100 ml pressure-flask. After 2 days' standing at room temp., the salt is washed several times with anhydrous benzene: 6·55 g (theoret. yield); m.p. 189–191°.[20]

Triphenylmethyl-^{14}C-phosphonium iodide (6·55 g, 16·5 mmoles) is dissolved in 25 ml of anhydrous ether (freshly distilled from phenylmagnesium bromide) in a 150 ml Schlenk-tube. Under a nitrogen atmosphere 15 mmole of phenyllithium—made from diphenylmercury[21] in 40 ml of anhydrous ether—is added. Stirring the mixture magnetically dissolves the salt within a few minutes. To this orange solution 1·04 g (18·0 mmoles) of anhydrous acetone in 10 ml of ether is added at −30°. The

* Very little change in product composition with pressure is observed in the reaction of *cis*- and *trans*-butene with diazomethane above a total pressure of 60 mm.[17]

[17] W. von E. Doering and D. MacDuffie, unpublished results.
[18] *Organic Syntheses* Coll. Vol. II, p. 165. Wiley, New York.
[19] R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer and C. E. Boord, *J. Amer. Chem. Soc.* **70**, 946 (1948).
[20] A. Michaelis and L. Gleichmann, *Ber.* 15, 810, (1882).
[21] W. Schlenk and J. Holtz, *Ber.* **50**, 262 (1917).

tube is sealed and the reaction mixture is homogenized by intensive shaking for 1 hr at room temp. A white product precipitates. The mixture is then heated for 20 hr at 70°; the tube is cooled in liquid nitrogen for 2 hr, opened and the 2-methylpropene—together with ca. 30% of ether and small amounts of acetone and benzene—is distilled with the use of a 20 cm "Podbielniak"-column. 2-Methylpropene is separated and purified by g.l.p.c. using a 10 ft "C"-column at 20°. The yield of 2-methylpropene varies between 60 and 70% on the basis of phenyllithium.

Ozonization of 2-methylpropene-1-^{14}C

2-Methylpropene-1-^{14}C (13·7 mg) is dissolved in 0·25 ml of purified pentane (shaken with sulfuric acid for several days), and cooled to −70°. A very small part of an ozone/oxygen stream, containing ca. 2·2 g of ozone per hr, is diverted through the methylpropene–pentane solution at −70° at a rate of ca. 1 bubble per second. As soon as the potassium iodide solution at the exit turns yellow, the oxidation is stopped, and the excess of ozone is expelled with a stream of dry nitrogen. Lithium aluminum hydride (20 mg) is added and the mixture is slowly warmed to 0°, 0·25 ml of anhydrous ether having been added in order to increase the solubility of the lithium aluminum hydride. The reaction starts vigorously and has to be cooled from time to time. It is finally kept at 0° for several hours. The mixture then is again cooled to −70° and decomposed by adding 20 mg of water. The decomposition is completed by warming up very slowly and shaking at 0° for 1 hr. The reaction vessel is attached directly to the g.l.p.c.-column and the crude mixture of ether, pentane, methanol, propanol-2 and water is introduced into the 5 ft "F"-column (tetraethyleneglycol–dimethylether on firebrick; at 50°) as quickly as possible by surrounding the flask by a bath at 220°. By fractionating two or three times the alcohols are obtained quite pure and give symmetrically shaped peaks. Radioactivity and mass are then assayed simultaneously. If the mixture is introduced into the column too slowly the peaks are very broad and prevent the radioactivity peaks from being cleanly separated and returning to the background level between peaks. The number of disintegrations N is integrated automatically and recorded on the activity chart. N is then related to the total absolute activity A by the equation $N = A(V/F_{H_e} + F_{M_e})$ where V is the volume of the counter and F_{H_e} and F_{M_e} are the flow rates (ml/min) of the carrier gases helium and methane, respectively. A counter of 12·87 ml volume was used in all our experiments. Since the precision of these determinations increases the larger N is and the larger R becomes relative to R_B (R being the average counting rate in counts/min and R_B being the background counting rate), low flow rates varying from 20–35 cc/min for the different runs were employed and the column was operated at the highest temp. consistent with satisfactory separation. It is evident that the precision of the determination of specific activities of the same material in different runs depends almost completely on the precision in achieving the same flow rates and the same operating temp. Since we have not been interested in absolute activity, we did not take special care to keep these variables constant in all experiments. As long, however, as the temp. and flow rates are kept constant within each single run, the ratio of the specific activities of the components will be constant for identical runs. In order to determine the specific activities, the corresponding peak areas on the mass chart are measured and translated into milligrams of substance on the basis of previous calibration experiments.

The sample of 2-methylpropene-1-^{14}C afforded: methanol, 5·8 mg, 435, 600 dpm: α: 40,050 dps/mmole. The activity of the propanol-2 was within the background.

Reaction between diazomethane and 2-methylpropene-1-^{14}C in the liquid phase

(a) *In dilute solution.* 2-Methylpropene-1-^{14}C (50 mg) is diluted with 450 mg of inactive material (Phillips, pure grade, 99%) and allowed to react in the described way with diazomethane from 10 g of nitrosomethylurea. 2-Methylpropene-1 (29·6 mg) recovered from this reaction, is purified on a 4 m "A"-column at 20° and a 10 ft "E"-column (dimethylformamide on firebrick) at 0° and degraded. Methanol and propanol-2 are fractionated three times on the 5 ft "F"-column at 50° and analyzed as described above. Methanol, 8·1 mg, 78, 120 dpm: α: 5280 dps/mmole; propanol-2, 50 mg (from two identical runs), 1846 dpm: α: 37 dps/mmole. (With this highly diluted starting material, any activity distribution in the 2-methylbutene-1 could not be detected. Therefore, additional experiments in concentrated solution were carried out).

(b) *Concentrated solution.* 2-Methylpropene-1-^{14}C (42·3 mg) is condensed with 10 mg of diazomethane and irradiated for 2 hr in a closed system. Diazomethane, 20 mg, is added in 2 portions and the irradiation continued for 2 hr in each case. Recovered 2-methylpropene (4·7 mg), purified

VOL. 6 1959

on the 10 ft "E"-column at 0° is ozonized and analyzed in the usual way: methanol, 0·4 mg, 34,160 dpm: α: 45,530 dps/mmole; propanol-2, 0·6 mg, 776 dpm: α: 906 dps/mmole.

2-Methylbutene-1, 2·7 mg, isolated from this run and purified on the 10 ft "E"-column at 0° is diluted with 2·2 mg of inactive material (Mathieson, 99% pure), ozonized and worked in the described manner: methanol and butanol-2, fractionated twice on the 5 ft "F"-column at 80° show the following activity: methanol, 1·6 mg, 64,180 dpm: α: 20,060 dps/mmole; butanol-2, 3·7 mg, 810 dpm: α: 170 dps/mmole.

Reaction between diazomethane and 2-methylpropene-1-^{14}C in the gas-phase

2-Methylpropene-1-^{14}C, 20·2 mg and 47·0 mg of inactive material is condensed with 50 mg of diazomethane in a 450 ml flask and irradiated for 2 hr under a partial pressure of purified nitrogen of 350 mm, the reaction flask being cooled with running water. Diazomethane, 50 mg, is added again and the irradiation continued for 2 hr more. The reaction products are separated and purified on the 10 ft "C"-column at 20° and the 10 ft "E"-column at 0°. (Besides the earlier described reaction products of the liquid-phase reaction, in this case, a small amount of radioactive 2-methylpropane was isolated and identified). 2-Methylpropene (20 mg) recovered and purified is degraded. The alcohols are fractionated three times on the 5 ft "F"-column at 50°: methanol, 3·9 mg, 99,930 *dpm*: α: 13,525 *dps*/mmole; propanol-2, 11 mg, 4627 dpm: α: 420 *dps*/mmole.

2-Methylbutene-1 (10·29 mg), isolated from two such runs, and purified on the 10 ft "E"-column at 0° is degraded and the alcohols fractionated at the 5 ft "F"-column at 80°: methanol, 3·2 mg, 62,610 *dpm*: α: 10,435 *dps*/mmole; butanol-2, 7·3 mg, 5320 *dpm*: α: 893 *dps*/mmole.

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VOL.
6
1959

THE MAGNITUDE OF ELECTRONIC ISOTOPE EFFECTS*

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Abstract—Secondary isotope effects, i.e. kinetic isotope effects in reactions where the bond to the labeled atom is not broken, are now being widely used for investigations of organic reaction mechanisms. In a recent paper, Halevi[1] has discussed secondary hydrogen isotope effects, and has suggested that there is an inductive contribution to such isotope effects. In particular, he suggests that there is more facile electron release from a C—D bond than from a C—H bond. The purpose of this communication is to examine in more detail some of the evidence cited by Halevi, and to estimate the theoretical limitations on such an effect.

Dipole moments

IN several cases, gas-phase dipole moment measurements have been made for the same compound containing either protium or deuterium.[2,3] Unfortunately, in most cases the difference caused by isotopic substitution is within the experimental error. There are two cases, however, where the emphasis was upon just this isotope effect: the comparison of HCl and DCl[4] ($\Delta\mu = 0{\cdot}003$–$0{\cdot}007$ D) and the comparison of NH_3 and ND_3[5] ($\Delta\mu = 0{\cdot}012$–$0{\cdot}015$ D). Bell[4] has shown that one can quantitatively predict the isotope effect on the dipole moment from independent data given by vibrational frequencies and intensities. This effect is caused by the anharmonic character of the normal vibrations. To see this qualitatively, consider the symmetric

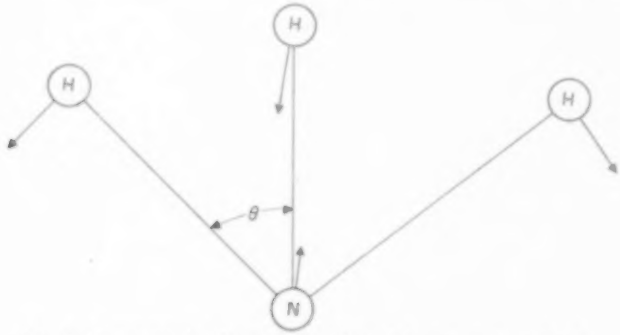

FIG. 1. Symmetric bending vibration (ν_2) of the ammonia molecule.

* Research performed under the auspices of the U.S. Atomic Energy Commission.

[1] E. A. Halevi, *Tetrahedron* **1**, 174 (1957).
[2] A. A. Maryott and F. Buckley, *Table of Dielectric Constants and Electric Dipole Moments of Substances in the Gaseous State*. National Bureau of Standards Circular 537, U.S. Government Printing Office, Washington, D.C. (1953).
[3] C. H. Townes and A. L. Schawlow, *Microwave Spectroscopy* Appendix VI. McGraw-Hill, New York (1955).
[4] R. P. Bell and I. E. Coop, *Trans. Faraday Soc.* **34**, 1209 (1938).
[5] J. M. A. deBruyne and C. P. Smyth, *J. Amer. Chem. Soc.* **57**, 1203 (1935).

bending mode of NH_3 (Fig. 1). The potential energy as a function of the interbond angle is of the form shown in Fig. 2, in which the lowest vibrational levels of NH_3 and ND_3 are indicated. Because this potential curve is not a parabola, the average interbond angle is larger for NH_3 than for ND_3, hence the former molecule is more nearly planar and has a smaller dipole moment.

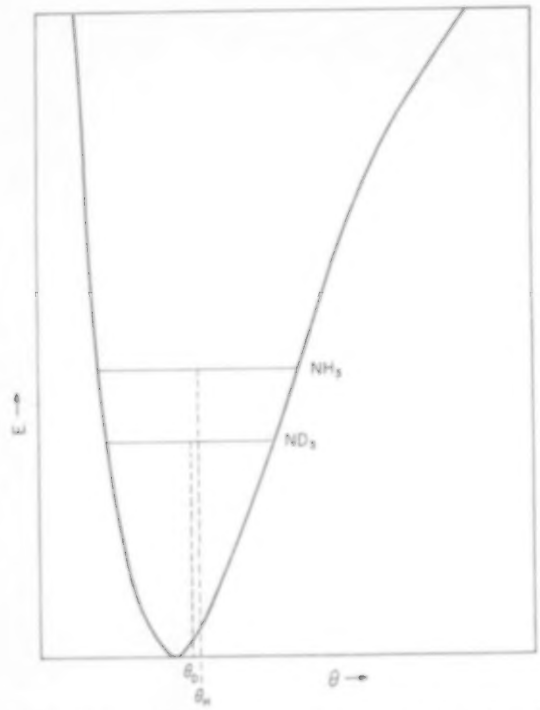

FIG. 2. Potential energy of the ammonia molecule as a function of interbond angle.

Nuclear quadrupole coupling constants

Again, there are a number of cases where the substitution of deuterium for protium changes the nuclear quadrupole coupling constant.[3,6] This constant is related to the second derivative of the molecular electric field at the "probe" nucleus, and thus to the electric charge distribution in the molecule. Because of molecular vibrations, the probe nucleus will measure some sort of average electric field derivative in a region surrounding its equilibrium position. Again, vibrational anharmonicities will cause the nucleus to map out slightly different regions for different isotopic species. This explanation was advanced by Simmons and Goldstein[7] to explain the difference in the halogen atom quadrupole coupling constants for CH_3X and CD_3X (X = Cl, Br, I). It may be noted that the relative shift produced by deuterium substitution is less for CH_3I than for CH_3Cl. This is reasonable in terms of the smaller vibrational amplitude of the heavier molecule, which should decrease the anharmonicity.

[6] J. Duchesne, *J. Chem. Phys.* **20**, 1804 (1952); *Ibid.* **25**, 369 (1956).
[7] J. W. Simmons and J. H. Goldstein, *J. Chem. Phys.* **20**, 122 (1952).

Chemical shifts in NMR spectra

The fluorine nuclear magnetic resonance spectra of n-C_3F_7D and n-C_3F_7H show a similar isotope effect.[8] The shielding of the fluorine atoms in the $—CF_2D$ group is 0·60 ± 0·05 p.p.m. greater than that for fluorine atoms in the $—CF_2H$ group, which indicates a greater effective electron density around the fluorine atoms in the former compound. The explanation is presumably similar to that for the effect on quadrupole coupling constants.

Kinetic isotope effects

The question which now arises is how one may account for the observed mass-sensitivity of certain electronic properties of a molecule in formulating the isotope effect on a reaction rate.

The current theoretical treatment of the effect of isotopic substitution on reaction rates was originated by Bigeleisen,[9] and is founded upon the absolute reaction rate theory of Eyring and others. The ratio of rate constants for two isotopic species is given by

$$k/k_i = (M_i^*/M^*)^{1/2}(Q^\ddagger/Q_i^\ddagger)(Q_i/Q) \quad (1)$$

In this formula, M* is an effective mass for motion along the reaction co-ordinate, while Q and $Q^\ddagger$ are partition functions of the original species and of the transition state, respectively. In the case of a secondary isotope effect, the contribution of the reduced-mass term is expected to be negligible. It has been shown[10] that the partition function ratios can be expressed in terms of the fundamental vibrational frequencies of the species involved, if the potential energy function is invariant to isotopic substitution. The suggestion of an inductive isotope effect implies that this last assumption is not correct, and that there is a mass effect on the electronic factor in the partition function, i.e. a shift in electronic levels in going from one isotopic species to another. The magnitude of such an effect may be estimated.

The only case which can be treated exactly is that of the hydrogen atom. For this simple case, the difference in electronic energy levels between H and D is caused by the very small difference in the reduced mass of the electron–proton system compared to that of the electron–deuteron system.[11] This amounts to 30 cm^{-1}, and exp (30 cm^{-1}/kT) is about 1·15 at 300°K. For more complex molecules, the corresponding many-body problem cannot be solved, and recourse is made to the Born–Oppenheimer approximation,[12] which makes it possible to solve separately the wave-equations for electronic and nuclear motion. According to this approximation, the interaction between these two types of motion, which is just the effect being considered, is proportional to the ratio of the electron mass to some sort of average nuclear mass for the molecule. Hence, in a molecule containing C, N, or O atoms, the effect of deuterium substitution is an order of magnitude smaller than the 30 cm^{-1} predicted for the difference between H and D atoms. The difference in this interaction effect between two molecules, e.g. the reactant and the activated complex, should be vanishingly small compared to possible differences in vibrational frequencies.

There is experimental evidence that an electronic effect of this type is unimportant.

[8] G. V. D. Tiers, *J. Amer. Chem. Soc.* **79**, 5585 (1957).
[9] J. Bigeleisen, *J. Chem. Phys.* **17**, 675 (1949).
[10] J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.* **15**, 261 (1947).
[11] H. C. Urey, *J. Chem. Soc.* 562 (1947).
[12] M. Born and J. R. Oppenheimer, *Ann. Physik* **84**, 457 (1927); T.-Y. Wu and A. B. Bhatia, *J. Chem. Phys.* **24**, 48 (1956).

Rossini, Knowlton, and Johnston[13] obtained precise calorimetric data for H_2O and D_2O. These results, combined with other experimental thermochemical data, enabled them to obtain the difference in the heats of formation at absolute zero of H_2O and D_2O. The same quantity can also be obtained from purely spectroscopic data, from the relationship

$$(\Delta H_{f0}^{\circ})_{H_2O} - (\Delta H_{f0}^{\circ})_{D_2O} = (E^{v}_{H_2O} - E^{v}_{D_2O}) - (E^{v}_{H_2} - E^{v}_{D_2}) \qquad (2)$$

in which E^v represents the vibrational zero-point energy. From suitable data for the isotopic hydrogen molecules[14] and for the isotopic water species,[15] one obtains a value of 617·0 cm^{-1}. The calorimetric data lead to a value of 613·5 $\pm$ 7·5 cm^{-1}, in excellent agreement. One must conclude either that electronic effects are absent, or that they are the same for hydrogen and water molecules.

Isotope exchange equilibria

Halevi's measurements[16] of the dissociation constant of phenylacetic acid and its analog deuterated in the methylene group show that the deuterium compound has a dissociation constant 0·895 as large as that of the protium compound. The comparison of these dissociation constants is equivalent to the isotope exchange equilibrium

$$Ph{\cdot}CD_2COOH + Ph{\cdot}CH_2COO^- = Ph{\cdot}CD_2COO^- + Ph{\cdot}CH_2COOH, K_{eq} = 0{\cdot}895. \qquad (3)$$

The equilibrium constant for such a reaction may be expressed in terms of partition functions analogous to those in equation (1).[10] If one ignores a possible explanation of this effect in terms of differences in vibrational zero-point energy, this is equivalent to the assumption that the C—H bonds in the methylene group are the same in both the acid and the anion. This is probably not so; in any case it is not so for acetic acid itself,[17,18] where some of the stretching frequencies are lower in the anion.[19] Also, the frequencies of some of the skeletal vibrations are changed by deuterium substitution in the acetate ion,[17] and these low frequencies will make a contribution to the entropy. Thus (and this is true for secondary isotope effects in general), small zero-point energy contributions may arise from differences in vibrational frequencies of the ground state and transition state even when the isotopically substituted atom has substantially the same bonding in both states, simply because the molecule is not a collection of independent diatomic oscillators.

If there are isotope effects caused by a difference in electron-releasing ability of hydrogen isotopes, one might look for such effects on hydrogen isotope exchange equilibria in general. In particular, such an effect would be expected in a molecule where hydrogen is bonded to a more electro-negative atom. Suitable examples are

$$HD + H_2O = H_2 + HDO \qquad (4)$$

and

$$HT + H_2O = H_2 + HTO. \qquad (5)$$

[13] F. D. Rossini, J. W. Knowlton and H. L. Johnston, *J. Res. Nat. Bur. Stand.* **24**, 369 (1940).
[14] G. Herzberg, *Spectra of Diatomic Molecules* Table 39. D. Van Nostrand, New York (1950). Values for HD were calculated from the more accurate data for H_2.
[15] W. F. Libby, *J. Chem. Phys.* **11**, 101 (1943).
[16] E. A. Halevi and M. Nusim, *Bull. Research Council Israel* **5A**, 263 (1956).
[17] L. H. Jones and E. McLaren, *J. Chem. Phys.* **22**, 1796 (1954).
[18] J. K. Wilmshurst, *J. Chem. Phys.* **25**, 1171 (1956).
[19] A. Streitweiser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Amer. Chem. Soc.* **80**, 2326 (1958).

Over a limited temperature range, the equilibrium may be written in the form $K = Ae^{B/T}$. Values for the parameters A and B have been calculated from suitable vibrational data for the isotopic hydrogen molecules[14] and the isotopic water molecules,[15] by use of the method of Bigeleisen and Mayer.[10] Experimental values were obtained by a least-squares treatment of the data of Suess[20] for the deuterium exchange, and data of Black and Taylor[21] for the tritium exchange. The comparison of calculated and experimental values is given below:

Reaction	A (calc)	A (exp)	B (calc)	B (exp)
(4)	0·7361	0·733 ± 0·009	480·6	470 ± 5
(5)	0·6206	0·623 ± 0·009	689·6	688 ± 4

The excellent agreement precludes any significant electronic effects.

In conclusion, all the evidence presented in favor of an electronic isotope effect is explicable on the basis of vibrational effects. According to the Born–Oppenheimer theory, interactions between electronic and nuclear motion must be vanishingly small for molecules of the sort involved in organic reactions. It is difficult to conceive of a kinetic experiment which could measure an electronic isotope effect separately from the usual vibrational effect.

[20] H. E. Suess, *Z. Naturf.* **4a**, 328 (1949).
[21] J. F. Black and H. S. Taylor, *J. Chem. Phys.* **11**, 395 (1943).

VOL.
6
1959

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METHYLATION OF ALCOHOLS WITH DIAZOMETHANE

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(*Received* 22 *September* 1958)

Abstract—Alcoholic hydroxyl groups were methylated by diazomethane in the presence of catalytic amounts of fluoboric acid (FBA). Primary aliphatic and unhindered secondary alcohols gave 84–98% yields of methyl ethers, while tertiary and moderately hindered secondary alcohols afforded lower yields. The order of reactivity in the methylation of the isomeric butyl alcohols, as determined in competition experiments, was $n > s > t$, and of the epimeric cholestanols, 3 $\beta(e) > 3\ \alpha(a)$. The highly hindered alcoholic hydroxyl groups of *iso*borneol was not methylated by the new reagent. The methylation of weakly acidic phenols was catalyzed by FBA. The new methylation reaction was used to prepare directly methyl ethers of desoxycorticosterone and of testosterone, and to convert ascorbic acid selectively to its 2:3:6-trimethyl ether.

THE well-known methylation of alcoholic hydroxyl groups with methyl halides, methyl arenesulfonates or dimethyl sulfate by the Williamson synthesis[1] and related procedures, requires strongly basic reaction conditions, and there seems to be no completely satisfactory general methylation procedure effective under neutral or mildly acidic conditions.

Diazomethane serves *par excellence* as the methylating agent for *acidic* hydroxyl groups. It reacts readily with carboxylic acids; the more weakly acidic phenols and enols are methylated only slowly, while alcoholic hydroxyl groups are generally not methylated at all by this reagent. A few exceptions are known, such as carbinols with electron-withdrawing groups in the α-position, which are methylated only with difficulty.[2] Aluminum alkoxides have been reported to catalyze the methylation of alcohols with diazomethane, but the authors stated that their method lacked general preparative value.[2] In our hands, β-cholestanol was not methylated by excess diazomethane in the presence of 11 mole per cent of aluminum *t*-butoxide in methylene chloride solution.

In principle, diazomethane in the presence of an acidic catalyst should methylate alcohols. However, the usual protonic acid, such as hydrochloric acid, is unsatisfactory as a catalyst, being itself consumed by reaction with diazomethane, because the intermediate methyldiazonium cation combines more rapidly with the acid anion than with the alcohol. Fluoboric acid (FBA), on the other hand, promised to serve as a useful methylation catalyst, as it would produce a relatively long-lived diazonium cation that would react with an alcohol as the nucleophile,‡[3] and it could be consumed

* On leave from the Technion Israel Institute of Technology, Haifa.

† Contribution No. 2391.

‡ Cf. the reaction of diazoacetate and ethanol with various mineral acids, particularly fluoboric acid, as catalysts.

[1] A. W. Williamson, *J. Chem. Soc.* **4**, 229 (1852).

[2] H. Meerwein and G. Hinz, *Liebigs Ann.* **484**, 1 (1930).

[2] J. D. Roberts, C. M. Regan and I. Allen, *J. Am. Chem. Soc.* **74**, 3679 (1952).

VOL.
6
1959

in reaction with diazomethane only by some process involving rupture of a B–F bond. We have investigated the methylation of alcohols with diazomethane using FBA as a catalyst, and have found that this reaction is quite generally applicable and proceeds, within the scope described in the sequel, in high yields under mild conditions.

Methylations of hydroxyl compounds were carried out at 0–25° by adding slowly a solution of diazomethane to a solution of the alcohol containing 0·6–8·5 mole per cent of FBA. The solvents used were diethyl ether or, preferably, methylene chloride. The methyl ethers of *n*-butanol, *n*-octanol, α- and β-cholestanol were formed in appreciably higher yields in the latter solvent and, in addition, the reactions with diazomethane took place more rapidly and required less catalyst.

The results of methylations of a number of representative alcohols and phenols are recorded in Table 1. The methyl ethers of primary or unhindered secondary alcohols were formed rapidly in high (84–98%) yields by this reaction as evidenced by the methylations of *n*-butanol, *n*-octanol, *cyclo*hexanol, cholesterol, α- and β-cholestanol. Tertiary alcohols, and moderately hindered secondary alcohols, reacted more slowly, yields were lower and the reaction was accompanied by polymethylene formation, which could be minimized by operating at lower temperatures.*

Competition experiments showed that the relative rates of methylation of the three isomeric butyl alcohols were in the ratio primary : secondary : tertiary = 2·2 : 1·3 : 1·0, and those of the epimeric cholestanols were in the ratio 3β(*e*) : 3α(a) = 1·3 : 1. The rate orders were in the expected direction, but the relatively small spread indicated that the FBA-catalyzed diazomethane methylation lacked high steric selectivity. However, the 5(secondary)hydroxyl and the 6(primary)hydroxyl groups in 2:3-dimethyl ascorbic acid (Ib) were sufficiently different in reactivity to allow selective methylation of the primary in presence of the secondary hydroxyl group. Thus, ascorbic acid (Ia) was first methylated to the 2:3-dimethyl ether (Ib) by diazomethane in ether–methanol in the usual manner[4] in the absence of a catalyst; without purification, the crude enediol–diether (Ib) was converted by diazomethane in methylene chloride in the presence of 1·5 mole per cent of FBA into a hitherto unknown trimethyl ascorbic acid. The new trimethyl ether was isolated in 45% overall yield and after purification melted at 99·5–101°, $[\alpha]_D^{25}$ +33° (H_2O). It was assigned the 2:3:6-trimethyl ascorbic acid structure (Ic) on the following evidence:

(a) the maximum at 234 mμ (log ε 4·0) in the ultraviolet spectrum of the 101° compound degenerated in alkaline solution to a shoulder adjacent to the terminal absorption, and was regenerated on acidification;†

(b) after treatment of the trimethyl ether with aqueous alkali and buffering to pH 7·5, the solution consumed one mole equivalent of sodium periodate;

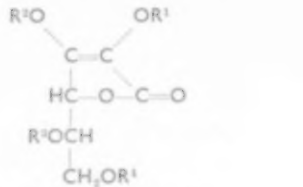
* The ethylation of secondary alcohols with FBA-catalyzed diazoethane, by an adaptation of the procedure described in the present paper, was used by W. I. Kimoto at Wisconsin to prepare *trans*- and *cis*-1-methyl-2-ethoxy*cyclo*pentane from the corresponding alcohols in 26% and 17% yields, respectively.

† These changes indicated formation of the carboxylate anion on opening of the lactone ring, and regeneration of the latter on acidification, as would be expected for a 2 : 3 : *x*-trimethyl ascorbic acid (Ic) in which the 6 (primary) hydroxyl group was blocked.[5]

[4] R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds and F. Smith, *J. Chem. Soc.* 1270 (1933).

[5] F. Micheel and W. Schulte, *Liebigs Ann.* **519**, 70 (1935); F. Micheel and G. Bischoff, *Ibid.* **525**, 66 (1936); W. N. Haworth, E. L. Hirst, F. Smith and W. J. Wilson, *J. Chem. Soc.* 829 (1937).

(c) the infrared spectral characteristics of the new compound were in accord with the structure (Ic).



Ia, $R^1 = R^2 = R^3 = H$
Ib, $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
Ic, $R^1 = R^2 = R^4 = CH_3$, $R^3 = H$

The hindered hydroxyl group of *iso*borneol could not be methylated by this method, even under forcing conditions. Triphenylcarbinol also failed to undergo methylation, perhaps because of preferential formation of triphenyl-carbonium fluoborate as evidenced by the color of the solution (halochromism).

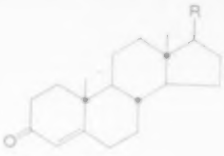
The new methylation reaction evidently occurs directly at the alcoholic oxygen atom with retention of the original configuration of the carbinol. The methyl ethers which are thus readily obtained are epimeric to those afforded, with inversion, by the alcoholysis of carbinyl tosylates and halides. For example, Nace[6] obtained α-cholestanyl methyl ether in 73% yield by methanolysis of β-cholestanyl tosylate, and the β-ether in 23% yield from the α-tosylate, together with olefins resulting from eliminations. On the other hand, the FBA-catalyzed diazomethane methylation afforded α-cholestanyl methyl ether from α-cholestanol, and the β-ether from β-cholestanol, in 98% yields, cf. Table 1. In contrast, cholesterol gave the same methyl ether[7] by each of the two paths. The nucleophilic solvolysis of cholesteryl tosylate (or chloride) proceeds by unimolecular substitution via a non-classical carbonium ion wherein the homoallylic π-electron center participates to effect overall retention of configuration.[8] The methylation of cholesterol by FBA-catalyzed diazomethane, however, proceeds undoubtedly *per se* with complete retention of configuration, without involving any part of the C_3–C_6 homoallylic system, as evidenced by the analogous steric course of methylation of the saturated cholestanols.

Newman and Beal[9] have reported that the formation of α-alkoxyketones from diazoketones and alcohols is catalyzed by boron trifluoride ethereate. We have found this reagent[10] also to be effective in catalyzing the methylation of alcohols with diazomethane. For example, the yield of β-cholestanol methyl ether was essentially unchanged by replacing the FBA catalyst with an equimolar amount of boron trifluoride etherate.

The new reagent provides a unique tool for the methylation of certain alcohols containing other sensitive groups. For example, in addition to the ascorbic acid case (see above), desoxycorticosterone (IIa) afforded directly 21-methoxyprogesterone

[6] H. R. Nace, *J. Amer. Chem. Soc.* **74**, 5937 (1952).
[7] W. Stoll, *Z. Physiol. Chem.* **207**, 147 (1932).
[8] C. W. Shoppee, *J. Chem. Soc.* 1147 (1946); S. Winstein and R. Adams, *J. Amer. Chem. Soc.* **70**, 838 (1948); E. M. Kosower and S. Winstein, *Ibid.* **78**, 4347, 4354 (1956).
[9] M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.* **72**, 5161 (1950).
[10] Since the manuscript of our preliminary communication, *J. Amer. Chem. Soc.* **80**, 2584 (1958), was written, similar observations were reported by E. Müller and W. Rundel, *Angew. Chem.* **70**, 105 (1958)

(IIb), while testosterone (IIc) gave the hitherto unknown 17β-methoxyandrost-4-ene-3-one (IId), m.p. 127–127·5°. These transformations are difficult, if not im-



IIa, R = $COCH_2OH$ IIc, R = OH
IIb, R = $COCH_2OCH_3$ IId, R = OCH_3

possible, by any previously known direct method of methylation.

The usually sluggish reaction of weakly acidic phenols with diazomethane was also shown to be catalyzed by FBA. Estradiol was thus converted directly to the dimethyl ether[11] in 81% yield under conditions which, although forcing, gave no reaction at all in the absence of the catalyst. Other weakly acidic phenols of p*K*a 9·5 to 10·2 gave poor to fair yields of methyl ethers.

EXPERIMENTAL*

Diazomethane (DM)

(*a*) *From* N-*nitroso*-N-*methylurea*. Solutions of diazomethane (DM) in diethyl ether, and in methylene chloride, were prepared by reported procedures.[12] The solutions were dried over potassium hydroxide pellets and the concentration of DM was determined by reaction of an aliquot with excess benzoic acid.

(b) *From* N-*nitroso*-N-*methyl*-N′-*nitroguanidine*. A modification of the procedure of McKay *et al.*[13] was used to prepare solutions of DM in methylene chloride. A slow stream of nitrogen was passed through the reaction flask to dilute the DM in the gaseous phase and to sweep it into the distillation and absorption assembly. Distillation of DM was discontinued when about 60–65% of the theoretical amount had been collected, while the distillate still showed a pale yellow color; thus the amount of water carried over from the reaction flask was minimized. All DM solutions were dried and analyzed as described above.

Fluoboric acid (FBA)

Concentrated FBA catalyst was used in all experiments listed in Table 1, as comparative methylation experiments with representative hydroxy compounds had shown that the yields of methyl ethers obtained in the presence of concentrated FBA catalyst were somewhat higher than with 50% aqueous FBA. Commercial FBA of ca. 50% concentration was concentrated further by partial evaporative distillation at 50–60°/5 mm. A pot residue of conc FBA thus obtained, which was ca. 16 N as determined by titration with standard alkali, was used in runs 1–4, 7 and 15–19 in

* All melting points of pure specimens are corrected for stem exposure. Ultraviolet spectra were determined with a Model 11 MS Cary Recording Spectrophotometer, and 95% ethanol was employed as solvent.

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[13] A. F. McKay, *J. Amer. Chem. Soc.* **70**, 1974 (1948); A. F. McKay, W. L. Ott, G. W. Taylor, M. N. Buchanan and J. F. Crooker, *Canad. J. Res.* **28B**, 683 (1950).

Table 1. Methylation of alcoholic and phenolic hydroxyl groups with diazomethane in the presence of fluoboric acid

Run	Hydroxy compound	mmoles	Diazo-methane, mmoles	Solvent[a]	Fluoboric acid mmoles	Methyl ethers based on hydroxy compound	% yield based on diazo-methane
	Primary alcohols						
1	*n*-Butyl alcohol	40·6	18·1	A	1·14		53[b]
2	*n*-Butyl alcohol	40·0	15·0	B	1·14		82[b]
3	*n*-Octyl alcohol	85·0	130·0	A	1·82	84[c]	55
4	*n*-Octyl alcohol	81·0	120·0	B	0·45	87[c]	59
5	L-Ascorbic acid	4·0	12·6[d]	[d]			
			5·8[e]	B	0·063	45[f]	31[g]
6	Desoxycorticosterone	0·3	1·0	B	0·0057	19	6
	Secondary alcohols						
7	*s*-Butyl alcohol	41·0	18·1	A	1·14		46[b]
8	*cyclo*Hexanol	90·0	120·0	B	0·91	92[c]	69
9	Cholesterol	1·0	3·43	B	0·0085	95[h]	28
10	α-Cholestanol	0·26	0·45	B	0·0057	65[h]	37
11	α-Cholestanol	0·26	1·26	B	0·0057	98[h]	20
12	β-Cholestanol	0·26	0·45	B	0·0057	70[h]	40
13	β-Cholestanol	0·26	0·82	B	0·0057	98[h]	31
14	Testosterone	8·0	17·6	B	0·68	22·5[i]	10
	Tertiary alcohols						
15	*t*-Butyl alcohol	40·8	18·1	A	1·14		39[b]
16	*t*-Butyl alcohol	14·3	29·0	A	0·80	45[b]	22
17	*t*-Amyl alcohol	11·4	14·3	B	0·34	66[b]	53
18	Dimethylphenyl-carbinol	45·0	90·0	A	1·82	30	15
	Competition experiments						
	n-Butyl alcohol	40·6					
19	*s*-Butyl alcohol	40·6	20·6	A	1·14	*n* : *s* : *t* =	
	t-Butyl alcohol	40·6				2·2 : 1·3 : 1·0[b]	
20	α-Cholestanol	0·26	0·75	B	0·0057	59[h] β : α = 1·3 : 1	
	β-Cholestanol	0·26				75[h]	
	Sec alcohol and phenol						
21	17β-Estradiol	1·0	5·0	B	0·026	25[j,k]	5
22	17β-Estradiol	0·5	10·7	B	0·02	81[j,k]	4
	Phenols						
23	Estrone	0·5	2·0	B	0·012	13[l]	4
24	Estrone	0·5	5·3	B	0·02	51[l]	5
25	*p*-Hydroxybiphenyl	0·5	5·3	B	0·0085	41[l]	4
26	1:3:5-Xylenol	1·0	10·2	B	0·0085	30[b]	3

[a] A = diethyl ether; B = methylene chloride. [b] Determined by vapor phase chromatography. [c] Isolated by fractional distillation. [d] Applied to ascorbic acid, in diethyl ether–methanol, without fluoboric acid. [e] Applied to 2 : 3-dimethyl ascorbic acid, without isolation, in B, in the presence of fluoboric acid. [f] Overall % conversion of ascorbic acid to 2 : 3 : 6-trimethyl ascorbic acid. [g] % yield calc. on second portion of diazomethane. [h] Isolated by adsorption chromatography. [i] 17β-Methoxyandrost-4-en-3-one. [j] Isolated by chemical separation and crystallization. [k] 17β-Estradiol dimethyl ether.

Table 1. This acid catalyst was added directly to the solutions of the alcohols methylated. In runs, 5, 6, 9–13 and 20–26, a 10·7 N FBA was used. This acid, prepared as described above, was made up to a catalyst stock solution A, containing 0·133 ml of the conc FBA in 25·0 ml of solution in 3 : 1 diethyl ether–methylene chloride.

Methylations of n-, s- *and* t-*butyl alcohols* (Runs 1, 2, 7 and 15, Table 1)

To a solution of the alcohol (40–41 mmoles) in 5·0 ml. of diethyl ether or methylene chloride was added 0·100 g (2·8 mole %) of FBA. The solution was cooled below 0° in a freezing mixture and a solution of DM in the appropriate solvent was added from a burette until ca. 0·4 mole equivalent had been added. The yellow color of DM was observed to disappear immediately on addition of the reagent to the alcohol solution. The reaction mixture was shaken with potassium hydroxide to neutralize the FBA, and some amorphous polymethylene was separated. The yields were determined by vapor phase chromatography (v.p.c.) on a column of dioctyl phthalate on Celite. The reaction mixtures from runs 1, 7 and 15 were subjected to v.p.c. directly, while that from run 2 was fractionally distilled before v.p.c. through a 55 cm Helipack column to remove two-thirds of the solvent. The identity of each graphically recorded main peak, and the relative amounts of alcohol and of methyl ether present in each of the reaction mixtures, were determined by comparison with standard solutions of the pure compounds. Peak areas were found to be proportional to concentrations to within 1% by weight.

A series of methylations, using the above procedure with equivalent amounts of 50% aqueous FBA instead of concentrated FBA catalyst, afforded lower yields of methyl ethers (*n*-butyl methyl ether, 49%; *s*-, 33%, *t*-, 31·5%).

Competition methylation of n-, s- *and* t-*butyl alcohols* (Run 19)

To a solution containing 40·6 mmoles each of *n*-, *s*-, and *t*-butyl alcohol and 0·07 ml (0·9 mole %) of concentrated FBA in diethyl ether was added 20·6 mmoles (0·17 mole equivalents) of DM in the same solvent. The relative amounts of the alcohols and of the methyl ethers in the reaction mixture were determined by v.p.c. The relative rates of methylation computed from these data were $n : s : t = 2{\cdot}2 : 1{\cdot}3 : 1{\cdot}0$.

Preparative methylations of alkyl-, cyclo*alkyl-, trialkyl- and dialkylarylcarbinols* (Runs 3, 4, 8 and 16–18)

The conditions used in the methylation of *n*-octyl alcohol, run 4, are representative for the general procedure which was also applied, with minor modifications, to the methylation of *cyclo*hexanol, *t*-butyl alcohol, *t*-amyl alcohol and dimethylphenylcarbinol. To a solution of 10·0 g of *n*-octyl alcohol in 20·0 ml of methylene chloride, containing ca. 0·023 g of conc FBA catalyst, which was cooled below 0°, was slowly added from a burette a solution of DM in methylene chloride. During the course of the reaction, a further portion of ca. 0·017 g of conc FBA catalyst was added. When 120·0 mmoles of DM had been added, a further portion of 0·5 g of *n*-octyl alcohol was added, which caused immediate decolorization of the excess of yellow DM present in the reaction mixture. The total amounts of reagents used represented a 1 : 1·5 molar ratio of the alcohol to DM. The FBA was removed with potassium hydroxide, and the solution was filtered to remove a small amount of polymethylene.

The solvent was removed by distillation and the residue was warmed for 45 min with metallic sodium to react with a small excess of the alcohol. The product was fractionally distilled to afford a first fraction of b.p. 53–65°/16 mm, which amounted to 0·80 g of somewhat impure *n*-octyl methyl ether as evidenced by its infrared spectrum; and a main fraction of pure methyl ether, b.p. 69–70°/18 mm, which amounted to 9·35 g (80·5%). The total yield of n-*octyl methyl ether* was 87%. An analogous methylation (run 3) of *n*-octyl alcohol in diethyl ether instead of methylene chloride, afforded a slightly reduced yield of methyl ether (84%), and required a considerably higher proportion of FBA catalyst (see Table 1).

The product obtained by methylation of *cyclo*hexanol in methylene chloride solution (run 8) by the above procedure gave on fractional distillation a first fraction of somewhat impure methyl ether, b.p. 35–52°/43 mm. The amount of cyclo*hexyl methyl ether* contained in this fraction was determined by infrared spectroscopy, and represented 9% yield. The main fraction of methyl ether, b.p. 52°/42 mm, amounted to 83% yield, the total yield being 92%.

The methylation of *t*-butyl alcohol in diethyl ether, run 16, by the same procedure, was accompanied by copious polymethylene formation. Analysis of the reaction mixture by v.p.c. indicated a 45% yield of t-*butyl methyl ether* and 46% of unreacted alcohol.

Dimethylphenylcarbinol was methylated in diethyl ether with a two-fold excess of DM (run 18). The reaction was slow and polymethylene formation was copious. Fractional distillation did not afford complete separation of the reaction mixture into pure components. The fractions obtained were analyzed by means of infrared and NMR techniques, and were found to contain a total amount of *dimethylphenylcarbinyl methyl ether* representing ca. 30% yield.

Attempted methylation of triphenyl carbinol

Triphenyl carbinol formed a deep orange-yellow solution, indicative of the presence of trityl ions, on addition of 16 N FBA catalyst in methylene chloride. To this solution was added a two-fold molar excess of DM solution in methylene chloride. The carbinol was recovered unchanged.

Methylations of sterols (Runs 9–13)

The following procedure, used in the methylation of β-cholestanol (run 13) is representative of the general conditions used, with changes in proportions of DM indicated in Table 1, also in the methylations of α-cholestanol and cholesterol. To a stirred solution of 0·100 g (0·26 mmole) of β-cholestanol, m.p. 142–142·5°, in 5·0 ml of methylene chloride, containing 0·1 ml (2·2 mole %) of FBA solution A, was added over a period of five min 2·40 ml of a 0·342 M solution of DM in methylene chloride, which had been cooled in a Dry Ice–acetone bath. This amount represented a 1 : 3·2 molar ratio of β-cholestanol to DM. The colorless reaction mixture, which contained very little polymethylene, was diluted with methylene chloride, filtered, washed with aqueous sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated to dryness in a stream of nitrogen and finally at reduced pressure (water aspirator). The methylation product was absorbed on a 60 × 10 mm column of 3·0 g of Florisil. The fractions eluted with 1 : 4 benzene–petroleum ether (b.p. 60–68°) amounted to 0·102 g (98%) of pure β-*cholestanyl*

methyl ether, m.p. 84–84·5°. The column was washed with diethyl ether to give a small fraction of 0·002 g of impure material, m.p. 77–93°. Methylation of cholesterol with a comparable excess (3·4 mole equivalents) of DM gave a 95% yield of the *methyl ether* (run 9), and the methylation of α-cholestanol with a larger excess (4·9 mole equivalents) of DM gave 98% yield of the respective *methyl ether* (run 11). Smaller excess amounts (1·7 mole equivalents) of DM afforded reduced yields of methyl ethers of α- and β-cholestanol (runs 10 and 12). Methylation of β-cholestanol by the above procedure, with 1·50 mole equivalents of DM, in the presence of concentrated FBA (2·2 mole %) and in the presence of an equivalent amount (2·2 mole %) of boron trifluoride etherate, afforded respectively, 38% and 33% yields of β-cholestanol methyl ether. Increase of the proportion of boron trifluoride etherate catalyst to 6·6 mole % lowered the yield of the methyl ether to 30%. Attempted methylation of β-cholestanol under the same conditions, but in the presence of 11·0 mole % of aluminum *t*-butoxide as the potential catalyst, did not produce any detectable amount of the methyl ether.

VOL. 6 1959

Competition methylations of α- and β-cholestanols (Run 20)

To a stirred solution containing 0·100 g (0·26 mmole) each of α- and β-cholestanol and 0·1 ml (1·1 mole %) of FBA solution A, was added over a period of 10 min 1·68 ml of a 0·445 M solution of DM in methylene chloride, which had been cooled in a Dry Ice–trichloroethylene cooling bath. The reaction mixture was worked up as described above. The quaternary mixture of unchanged epimeric cholestanols and of their methyl ethers was separated by chromatography on 10·0 g of Florisil. Elution with petroleum ether (b.p. 60–68°) afforded 0·061 g (59%) of α-cholestanol methyl ether, m.p. 60·5–62°, which was recrystallized from acetone–methanol to give 0·042 g of plates, m.p. 62–63°. Further elution with petroleum ether (b.p. 60–68°) to 3 : 17 benzene–petroleum ether (b.p. 60–68°) afforded 0·078 g (75%) of β-cholestanol methyl ether, m.p. 80–82°, which after recrystallization from methanol afforded 0·066 g of large plates, m.p. 84–85°. Elution with 3 : 7 benzene–petroleum ether (b.p. 60–68°) gave 0·036 g of recovered α-cholestanol, m.p. 180·5–182·5°, and elution with 1 : 1 benzene–diethyl ether afforded 0·022 g of recovered β-cholestanol, m.p. 138·5–141°, which after recrystallization from absolute ethanol gave 0·016 g of large plates, m.p. 141–142°.

2:3:6-*Trimethyl* L-*ascorbic acid* (Run 5)

A modification based on the procedure of Herbert *et al.*[4] was used to prepare 2:3-dimethyl-ascorbic acid. To a stirred suspension of 0·704 g (4·0 mmoles) of L-ascorbic acid (U.S.P., m.p. 190°) in a mixture of 3·0 ml of anhydrous methanol and 15·0 ml of anhydrous diethyl ether, cooled to −5 to −10°, was added during a period of 40 min 12·0 ml of a 0·465 M solution of DM in methylene chloride. At this stage of the reaction, evolution of nitrogen became slow, and it was reactivated by the addition of 5·0 ml of anhydrous methanol followed by 15·0 ml of DM solution over a period of 1 hr. The reaction mixture was kept for 15 hr at 25°, filtered, and the solvents were removed at reduced pressure (water aspirator). The crude enediol (0·811 g of a viscous syrup) was methylated further in the presence of FBA catalyst. To a stirred solution of the total enediol in 12·0 ml of methylene chloride, cooled to 0° and containing 0·25 ml of FBA solution A, was added 6·0 ml of the 0·465 M DM

solution over a period of 20 min. The evolution of nitrogen became slow at this stage, and a further portion of 0·1 ml of FBA solution A was added to the reaction mixture. Then the following successive portions of DM and FBA solutions were added: 2·0 ml of DM, 0·25 ml of FBA, 2·5 ml of DM, 0·25 ml of FBA, 2·0 ml of DM, and 0·25 ml of FBA solution A. The total amounts of reagents used were thus 5·8 mmoles of DM and 1·6 mole % of FBA catalyst added over a total period of 45 min. The reaction mixture was filtered, the amorphous residue of polymethylene was washed with a small amount of ethyl acetate, and the solvents from the combined filtrates were removed at reduced pressure (water aspirator). The syrupy crude product was dissolved in ethyl acetate, a small amount of diethyl ether was added, and the solution was seeded with 2:3:6-trimethyl ascorbic acid from an earlier run. The solution was kept for four days at —10°. It afforded clusters of fine prisms, 0·196 g (first crop), m.p. 95–98°. The mother liquor was concentrated to a syrup, and the crystallization procedure was repeated to afford 0·166 g (second crop) of prisms, m.p. 93–95°, and 0·030 g (third crop) of prisms, m.p. 88–91·5°. The combined crops, 0·392 g (45% overall yield from L-ascorbic acid) were recrystallized from ethyl acetate to afford long, slender prisms, 0·252 g (first crop), m.p. 99·5–100·5°, and 0·044 g (second crop), m.p. 99–100°. The first crop material was recrystallized twice from ethyl acetate to afford long prisms of 2 : 3 : 6-trimethylascorbic acid, m.p. 99·5–101°, $[\alpha]_D^{25}$ +33 (H_2O), λ_{max} 234 mμ (log ϵ 4·0), λ_{max}^{mull} 5·74 μ (α,β-unsat. γ-lactone), 6·01 (conj. C=C).

(Found: C, 49·5; H, 6·5, OCH_3, 42·3; Calc. for $C_9H_{14}O_6$: C, 49·54; H, 6·47; OCH_3, 42·67%).

2 : 3 : 6-Trimethylascorbic acid gave negative Fehling and ferric chloride tests.

To a solution of 3·2 mg of 2 : 3 : 6-trimethylascorbic acid in 10·0 ml of 40% aqueous ethanol was added 5 drops of 5% aqueous potassium hydroxide and the solution was heated to 90° for 1 hr. The ultraviolet spectrum of this solution showed only a shoulder at 233 mμ, adjacent to terminal absorption. This solution was acidified to pH2 with 5 drops of dilute hydrochloric acid and kept for 22 hr at 25°. λ_{max} 234 mμ (log ϵ 4·0).

Periodate cleavage of 2:3:6-*trimethylascorbic acid*

A solution of 10·3 mg of 2:3:6-trimethylascorbic acid (0·047 mmole) in 1·0 Ml of 1 N potassium hydroxide was heated on a steam bath for 10 min. The solution was diluted with 3·0 ml of water and heating was continued for an additional 20 min. The solution was cooled and adjusted to pH 7·5 with dilute acetic acid and sodium bicarbonate solutions. To the slightly basic solution was added 5·0 ml of a 0·08 M solution of sodium metaperiodate and the total volume was made up to 10·0 ml. After 2 hr the excess of periodate was determined by the usual sodium arsenite–iodine titration method, and 1·1 moles of periodate per mole of trimethylascorbic acid were found to have been consumed.

21-*Methoxyprogesterone* (Run 6)

To a stirred solution of 0·100 g (0·3 mmole) of desoxycorticosterone, m.p. 136–138,° in 5·0 ml of methylene chloride, containing 0·1 ml (1·9 mole %) of FBA solution A, was added over a period of 6 min 2·94 ml of a 0·342 M solution of DM in methylene chloride. The colorless reaction mixture was diluted with ether, filtered, washed with

aqueous sodium bicarbonate and water, and evaporated at reduced pressure (water aspirator). The residue was dried by the addition of benzene followed by evaporation again at reduced pressure. The infrared spectrum of the crude crystalline reaction product, m.p. 129–135°, showed no band in the OH stretching region. The product was chromatographed on 4·0 g of acid-washed alumina. Benzene eluted a crystalline middle fraction, 0·020 g (19% yield), m.p. 156–157°, which on recrystallization from methanol afforded 0·014 g (first crop) of the methyl ether, m.p. 158·5–159·5° (reported[14] m.p. 161–165°, m.p. 162–163°), λ_{max} 240 mμ (log ϵ 4·20); and 0·004 g (second crop), m.p. 156–158°. An earlier fraction of 0·009 g, m.p. 143–145°, eluted with 1 : 1 benzene–petroleum ether (b.p. 60–68°), and a later fraction of 0·037 g, m.p. 110–120°, eluted with diethyl ether, also contained substantial proportions of the methyl ether, as evidenced by their ultraviolet and infrared spectra. The yield in this reaction can undoubtedly be improved by modifying the conditions.

VOL. 6 1959

Testosterone methyl ether (Run 14)

To a stirred solution of 2·30 g (8·0 mmoles) of U.S.P. testosterone, m.p. 154–155°, in 25·0 ml of methylene chloride, containing 0·1 ml of catalyst stock solution of 0·200 g of concentrated FBA in 1·0 ml of dry diethyl ether, was added, at a rate of ca 2·0 ml per min 20·0 ml of a 0·345 M solution of DM in methylene chloride. This solution was kept cold during the addition by means of a "cold finger" filled with Dry Ice, which was immersed in the dropping funnel containing the DM solution. After the addition was complete two further 0·1 ml portions of catalyst solution were introduced at 5-min intervals, followed by a further 31-ml portion of DM solution. The total amounts of DM was thus 17·6 mmoles, and of FBA, 0·68 mmole. The reaction mixture was stirred for 20 min after addition of DM was complete. It was diluted with methylene chloride, filtered, the filtrate was washed with water, aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure to afford 2·42 g of a pale yellow viscous syrup, λ_{max} 241 mμ (log ϵ 4·1). The infrared spectrum showed only a slight band in the OH stretching region. The crude methylation product was chromatographed on 120 g of Florisil on a 30 × 400 mm column. The middle fractions eluted with 1 : 99 to 1 : 32 acetone–petroleum ether (b.p. 60–68°) afforded a total of 0·477 g of prisms, m.p. 112–115°. Crystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 0·378 g (first crop) of prisms, m.p. 126·6–126·9°. Recrystallization from the same solvent mixture yielded 0·287 g of prisms, m.p. 127–127·5°, $[\alpha]_D^{25}$ +106·3 ($CHCl_3$). λ_{max} 241 mμ (log ϵ 4·22), $\lambda_{max}^{CCl_4}$ 5·99 μ (C=O), 6·18 μ (C=C), 9·09 μ (ether—O—).

(Found: C, 79·2; H, 9·7; OCH_3, 10·6; Calc. for $C_{20}H_{30}O_2$: C, 79·42; H, 10·0; OCH_3, 10·26%).

Earlier fractions, amounting to 0·150 g, m.p. 105–112°, that were eluted from the column with 1 : 99 acetone–petroleum ether (b.p. 60–68°), and a later fraction, amounting to 0·080 g, m.p. 103–108°, eluted with a 1 : 36 ratio of the same solvents, were combined with the total residues from the crystallizations described above and rechromatographed. An additional 0·259 g of recrystallized tetosterone methyl ether, m.p. 127–127·5° was thus obtained (total yield 22·5%). Later fractions from

[14] C. Meystre and A. Wettstein, *Helv. Chim. Acta* **30**, 1256 (1947); H. Heusser, C. R. Engel and P. A. Plattner, *Ibid.* **32**, 2475 (1949).

the original chromatogram that were eluted with 1 : 13 acetone–petroleum ether (b.p. 60–68°) afforded 0·669 g of starting material, m.p. 146–148°, which after recrystallization from acetone gave 0·510 g, m.p. 152–153·5°.

17β-*Estradiol dimethyl ether* (Run 22)

To a stirred suspension of 0·136 g (0·5 mmole) of estradiol, m.p. 175–177°, in 25·0 ml of methylene chloride, containing 0·25 ml of FBA solution A, was added, over a total period of 17 min, 10·5 ml of a 0·445 M solution of DM in methylene chloride, followed by a further portion of 0·1 ml of FBA solution A and 13·5 ml of the DM solution. A considerable amount of amorphous polymethylene, which was present in the colorless reaction mixture, was removed by filtration and washed with methylene chloride. The combined filtrates were washed with aqueous sodium bicarbonate, potassium hydroxide, and water, and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the residue crystallized from absolute ethanol to afford 0·108 g of needles (first crop), m.p. 157·5–158·5°, and 0·023 g of needles (second crop), m.p. 150–152°. Two recrystallizations of the latter material from absolute ethanol afforded 0·012 g of needles, m.p. 157–158·5°. The total yield of 17β-estradiol dimethyl ether of good quality was 80%. A further recrystallization of the combined crops melting at 157–158·5° gave 0·101 g of needles, m.p. 160·5–162° (reported,[11] m.p. 161–162°). A control experiment, under identical conditions, but without the FBA catalyst, afforded complete recovery of the 17β-estradiol.

The above procedure is also representative of the general conditions used, with changes indicated in Table 1, in the methylation of estrone (run 24).

p-*Methoxybiphenyl* (Run 25)

To a stirred solution of 0·085 g (0·5 mmole) of *p*-hydroxybiphenyl, m.p. 163–164°, in 12·0 ml of methylene chloride, which contained 0·15 ml of FBA solution A, was added 12·0 ml of a 0·445 M solution of DM in methylene chloride over a period of 9 min. The colorless reaction mixture, containing a considerable amount of amorphous polymethylene, was filtered and the solid was washed with methylene chloride. The combined filtrates were washed with aqueous sodium bicarbonate solution and with water and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure, and the residue was digested with 5% aqueous potassium hydroxide. The insoluble portion was washed with water, dissolved in methylene chloride, and the solution was dried over anhydrous sodium sulfate. Evaporation of the solvent at reduced pressure left 0·038 g (41% yield) of colorless plates, m.p. 78–80°. The *p*-methoxybiphenyl was purified by recrystallization from ethanol to give 0·022 g (first crop) of plates, m.p. 85–87° (reported,[15] m.p. 90°), and 0·012 (second crop) of plates, m.p. 74–76°. From the aqueous potassium hydroxide solution there was recovered by acidification and extraction 0·048 g (56% recovery) of *p*-hydroxybiphenyl, m.p. 163–165°.

1-*Methoxy*-3:5-*xylene* (Run 26)

The methylation of 1:3:5-xylenol, m.p. 63–65°, was carried out under conditions based on the preceding experiment, using the amounts of reagents given in

[15] A. Werner, B. Löwenstein, A. Wack, T. Frey, M. Kunz, K. Rekner, A. Ney, H. Heil, A. Scherrer, H. Schwabacher and A. Grob, *Liebigs Ann.* **322**, 135 (1902).

Table 1. The methylation mixture, after removal of the solvent, was subjected to v.p.c. on a 40 ft column of 20% Dow Corning 550 Fluid on Johns–Manville C22 firebrick. The separation of the unchanged 1 : 3 : 5-xylenol from its methyl ether was not complete. The relative peak areas were estimated to be in the ratio 1:3:5-xylenol:1-methoxy-3 : 5-xylene = 7 : 3.

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VOL.
6
1959

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THE CONSTITUTIONS OF ATROVENETIN AND OF SOME RELATED HERQUEINONE DERIVATIVES

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Abstract—Deoxy*nor*herqueinone and atrovenetin have been shown to be identical. On the basis of spectral evidence these compounds, and related substances, have been characterised as substituted 9-hydroxyperinaphthenones. This conclusion has been confirmed by oxidative degradation to the appropriate naphthalic anhydrides as well as by further oxidation to nitrococussic acid. The constitution of an important oxidation product, $C_{15}H_{14}O_9N_2$, obtained by the action of nitric acid on atrovenetin has been established. On the basis of this and other evidence the constitutions of atrovenetin and certain of its transformation products have been elucidated.

ATROVENETIN, $C_{19}H_{18}O_6$, was isolated from *Penicillium atrovenetum* by Neill and Raistrick[1] who characterised it by a large number of derivatives and obtained several important degradation products. The morphologically closely related species, *P. Herquei* Bainier and Sartory, contains, as colouring pigments, the substances herqueinone, $C_{19}H_{17}O_6$ (OMe) and *nor*herqueinone, $C_{19}H_{18}O_7$,[2,3,4] and in view of the similarity in the empirical formulae some relationship was to be suspected. However, whereas atrovenetin shows aromatic stability herqueinone does not. Deoxyherqueinone, obtained by zinc and acetic acid reduction of herqueinone,[3] on the other hand, has this stability. By comparison of their respective triacetates (Experimental), it has now been shown[5] that deoxy*nor*herqueinone, obtained in a similar manner from *nor*herqueinone, is identical with atrovenetin. Data derived from the chemistry of herqueinone is thus pertinent to structural work on atrovenetin.

Prior knowledge[1] as to the functional groups of atrovenetin may be summarised as follows. Atrovenetin contains a minimum of four hydroxyl groups (formation of tetramethyl ethers). On the basis of a carbonyl absorption band in the infra-red at about 1630 cm^{-1} (Table 1) a further oxygen atom was probably present as an inert (hydrogen bonded) conjugated carbonyl group. Since the tetramethyl ethers were insoluble in alkali the remaining oxygen function was probably ethereal. Atrovenetin contains 2–3 C-Methyl groups (Kühn–Roth).

With the deoxy*nor*herqueinone-atrovenetin identity established further conclusions with regard to this ethereal oxygen may be reached. Since, on acid hydrolysis, herqueinone and *nor*herqueinone give xanthoherquein $C_{15}H_{12}O_7$ and *nor*xanthoherquein $C_{14}H_{10}O_7$, respectively, both of which are optically inactive, together with methyl *iso*propylketone[3,4], it must be concluded that *nor*xanthoherquein represents the atrovenetin nucleus whilst the expelled five-carbon fragment contains both the original ethereal oxygen atom and the asymmetric centre responsible for the optical

[1] K. G. Neill and H. Raistrick, *Biochem. J.* **65**, 166 (1957).
[2] F. H. Stodola, K. B. Raper and D. I. Fennell, *Nature, Lond.* **167**, 773 (1951).
[3] J. A. Galarraga, K. G. Neill and H. Raistrick, *Biochem. J.* **61**, 456 (1955).
[4] R. E. Harman, J. Cason, F. H. Stodola and A. L. Adkins, *J. Org. Chem.* **20**, 1260 (1955).

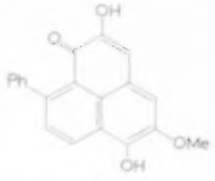
VOL. 6 1959

TABLE 1

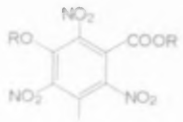
Hydroxyperinaphthenones

Compound	Bands (cm^{-1}) in Nujol		
Atrovenetin (IX)	1620	1570	
Perinaphthenone	1637	(1620)	1582
9-Hydroxyperinaphthenone	1625	1585	
Xanthoherquein			1600 (broad)
Product obtained by $LiAlH_4$ redn. of (XII; R = H)	1630	1582	
Product obtained by $LiAlH_4$ redn. of (XI; R = H)	1620	1577	
Atrovenetin 'orange' trimethyl ether, (XII; R = H)	1613	1557	
Atrovenetin 'yellow' trimethyl ether, (XI; R = H)	1607	1590	
Atrovenetin tetramethyl ether A, (XII; R = Me)	1630	1577	
Atrovenetin tetramethyl ether B, (XI; R = Me) or (XIII)	1613	1600	

activity of atrovenetin. These conclusions have been substantiated. In particular, a close resemblance in ultra-violet spectra was apparent between the relevant derivatives of xanthoherquein, *nor*xanthoherquein, and atrovenetin (Table 2) suggesting the presence of a similar nucleus. The spectra also resembled the specially characteristic spectrum of 9-hydroxyperinaphthenone (Table 2).[5] At this time no naturally occurring perinaphthenone was known, but since then the isolation and characterisation of haemocorin[6] (I or equivalent tautomer) has been recorded.



I



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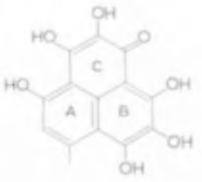

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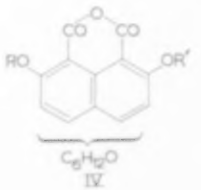

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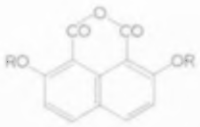


V

[5] D. H. R. Barton, P. de Mayo, G. A. Morrison, W. H. Schaeppi and H. Raistrick, *Chem. & Ind.* 552 (1956).
[6] R. G. Cooke and W. Segal, *Aust. J. Chem.* **8**, 107, 413 (1955); R. G. Cooke, Johnson and W. Segal, *Ibid.* **11**, 230 (1958).

Table 2

Compound	$\lambda\lambda_{max}$ (mμ) intensity (log ε) in parentheses						λmin. (mμ) intensity (log ε) in parentheses
9-Hydroxyperinaphthen-1-one	235 (4·38)	260 (3·92)	352 (4·26)	395(infl.) (3·68)	415 (3·95)	438 (4·05)	280 (2·97)
Deoxy*nor*herqueinone triacetate*	247(infl.) (4·28)	276 (4·19)	348–51 (4·07)	390(infl.) (4·00)	407–10 (4·18)	433 (4·27)	298 (2·81)
Atrovenetin triacetate†	247(infl.) (4·23)	275 (4·23)	347–50 (4·08)	390(infl.) (4·01)	409 (4·20)	433 (4·29)	298 (2·80)
Deoxyherqueinone diacetate	c.250(infl.) (4·27)	278 (4·10)	358 (4·20)	389 (4·09)	410 (4·18)	433 (4·23)	294 (2·54)
Xanthoherquein tetracetate	240 (4·39)	267 (4·00)	375 (4·28)		420 (4·03)	445 (3·97)	292 (3·08)
*nor*Xanthoherquein pentacetate	242 (4·44)	266(infl.) (4·12)	370 (4·28)		415 (4·03)	440 (4·03)	298 (2·93)
Perinaphthenone		248 (4·34)	315 (3·58)	360 (4·02)	384 (3·95)		275 (2·95)
Atrovenetin, (IX)	222 (4·25)	250–260(infl.) (4·26)			385 (4·21)	410-20(infl.) (4·10)	310 (2·74)
Deoxyherqueinone, (XVII; R = H, R′ = Me) or (XVII; R = Me, R′ = H)		250–265(infl.) (4·26)			385(infl.) (4·22)	405	300 (3·17)
Xanthoherquein	216	255(infl.) (4·19)			395 (4·19)	410(infl.) (4·17)	305 (3·22)
Product obtained by $LiAlH_4$ reduction of (XI; R = H)′	220 (4·31)	239 (4·36)	272 (4·40)	340 (3·96)		422 (4·14)	300 (2·90)
Product obtained by $LiAlH_4$ reduction of (XII; R = H)′	220 (4·48)		275 (4·56)	342 (3·97)		438(4·27) 462(4·25)	295 (3·00)

* Additional inflection at 260–65 mμ log ε = 4·16
† Additional inflection at 265 mμ log ε = 4·15

With these facts in mind the degradation of xanthoherquein was attempted to confirm or disprove the hydroxyperinaphthenone nature of the nucleus. By heating on the steam bath with concentrated nitric acid nitrococussic acid (II; R = H)[7] was formed. This was characterised as the methyl ester methyl ether, and by decarboxylation[8] to 2:4:6-trinitro-*m*-cresol, the latter and its methyl ether being compared with authentic specimens. The genesis of (II; R = H) is most simply explained if two of the nitro groups are introduced by electrophilic decarboxylative nitration.[9] Its formation finds close analogy in the production of the same compound by the nitration of carminic acid.[7,8] If *nor*xanthoherquein is to be formulated as a perinaphthenone, then nitrococussic acid (II; R = H) must represent that ring which bears the methyl group and which has only one phenolic hydroxyl group. Since *nor*xanthoherquein has seven oxygen atoms attached to the nucleus it follows that every carbon atom in the nucleus must be attached to oxygen except the angular and central carbons and the C-Me, and the C-H (substituted to C-NO_2 in (II, R = H)) characterised in the formation of the nitrococussic acid. *nor*Xanthoherquein must, therefore, be (III) or equivalent tautomer. Nitrococussic acid was also obtained by similar oxidation of *nor*xanthoherquein and of atrovenetin.

[7] W. de la Rue, *Liebigs Ann.* **64**, 1 (1848).
[8] C. Liebermann and W. A. van Dorp, *Liebigs Ann.* **163**, 97 (1872).
[9] E. Grovenstein Jr., and U. V. Henderson, Jr., *J. Amer. Chem. Soc.* **78**, 569 (1956).

VOL.
6
1959

Our attention was next turned to the oxidative degradation of atrovenetin itself in an endeavour to determine whether the ether bridge was attached to ring C or ring B, (III). By very brief oxidation with alkaline hydrogen peroxide followed by chromatography on paper powder a substance, $C_{18}H_{16}O_8$, was obtained. This was optically active, could also be prepared by chromic acid oxidation of deoxyherqueinone and gave a diacetate on mild acetylation. This compound was assigned the part structure (IV; R = R′ = H) for the following reasons. First, the infra-red spectrum (Table 3) showed carbonyl bonds close to those found for 2:7-dihydroxynaphthalic anhydride (V; R = H), whilst those of the corresponding diacetate closely resembled the appropriate bonds in the spectrum of 2:7-diacetoxynaphthalic anhydride (V; R = Ac) and of naphthalic anhydride itself. Naphthalic anhydrides have, of course,[10] very characteristic infra-red bands. Secondly, the $C_{18}H_{16}O_8$ anhydride, its diacetate, and the authentic naphthalic anhydride derivatives all exhibited a strong blue fluorescence in ultra-violet light said to be characteristic of a C—O—C bridge in the peri-position of naphthalene.[11]

The remarkable difference between the position of the infra-red carbonyl bands in the anhydride and its diacetate, paralleled by a similar change between the spectrum of (V; R = H) and (V; R = Ac), is to be attributed to hydrogen bonding of hydroxyl and carbonyl groups on *both* sides of the anhydride ring as in (IV; R = R′ = H). That this was so was confirmed by a study of a product, $C_{19}H_{18}O_6$, obtained by oxidation of atrovenetin 'yellow' trimethyl ether[1] with chromium trioxide. This compound must be presented as (IV; R = Me; R′ = H) since it gave the naphthalic anhydride (IV; R = R′ = H) on demethylation with pyridine hydrochloride. By a similar oxidation of atrovenetin 'orange' trimethyl ether[1] a second methyl ether anhydride (IV; R = H; R′ = Me), which also gave (IV; R = R′ = H) on demethylation with pyridine hydrochloride, was obtained. The evidence for the orientation of the methoxyl groups in these anhydrides is presented later in the paper. The infra-red bands of the anhydrides from the 'yellow' and 'orange' trimethyl ethers are instructive (Table 3) and show clearly the hydrogen bonding effect of the *ortho*-hydroxyl group present in *both* isomers. It should be mentioned that the 'oxime' formed[1] by the anhydride from the 'yellow' trimethyl ether is now to be formulated as the derived N-hydroxyimide.[12]

The evidence so far presented restricts the attachment of the ethereal ring of atrovenetin to the two possibilities indicated in (VI) and (VII). A distinction between these two formulae was reached on the following evidence. By the nitric acid oxidation of atrovenetin Neill and Raistrick[1] obtained a phenolic product, $C_{15}H_{14}O_9N_2$, ($\lambda\lambda_{max}$ 263 and 344 mμ; log ε, 4·07 and 4·09 respectively) characterised by methylation with diazomethane to a monomethyl derivative. For this substance we propose the constitution (VIII; R = Me; R′ = R″ = H) on the following grounds.

First, the compound contains the moiety responsible for the nitrococussic acid formation, a simultaneous process in this degradation. Secondly, the structure adequately rationalises the stability of the molecule to such drastic oxidative conditions. Thirdly, the substance shows bands in the carbonyl region of the infra-red (Nujol) at 1785 (γ-lactone) and at 1740 (phthalide ring[13]) cm^{-1}. Fourthly, by treatment

[10] R. G. Cooke, *Chem. & Ind.* 142 (1955).
[11] H. E. French and J. E. Kircher, *J. Amer. Chem. Soc.* **66**, 298 (1944).
[12] D. E. Ames and T. F. Grey, *J. Chem. Soc.* 3518 (1955).
[13] F. D. Greene, *J. Amer. Chem. Soc.* **78**, 2250 (1956).

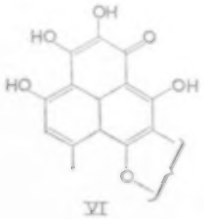
Table 3

Naphthalic anhydrides

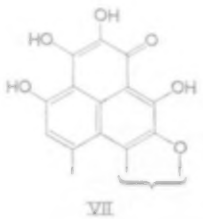
Compound	Bands (cm^{-1}) in Nujol	
Naphthalic Anhydride	1765	1735
2:7-Diacetoxynaphthalic anhydride (V; R = Ac)	1760 (broad)	1720
2:7-Dihydroxynaphthalic anhydride (V; R = H)	1720	1685
2:7-Dimethoxynaphthalic anhydride (V; R = Me)	1750	1720
*Anhydride (X; R = R′ = H)	1703	1660
Anhydride diacetate† (X; R = R′ = Ac)	1750	1720
Anhydride (X; R = Me, R′ = H) (from the 'yellow' trimethyl ether)	1750	1663
Anhydride (X; R = H, R′ = Me) (from the 'orange' trimethyl ether)	1747	1670

* Also in 1% $CHCl_3$ solution. (This indicates the absence of intermolecular hydrogen bonds.)
† This compound also showed absorption at 1773 cm^{-1} due to aromatic acetyloxy groups.

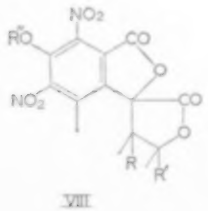
with base followed by methylation with diazomethane the phenol gave a methyl ether methyl ester. This showed bands in the infra-red (Nujol) at 1785 (γ-lactone) and at 1740 cm^{-1}. The latter band is to be attributed to the methyl ester and although high for a normal aromatic ester is to be compared with a band at 1740 cm^{-1} (in Nujol) found for methyl nitrococussate. Fifth, the structure (VIII) still retains the asymmetric carbon atom of atrovenetin and is compatible with the optical activity of the phenol. Finally, the ultra-violet spectrum of the phenol methyl ether (VIII; R = R″ = Me, R′ = H) was very similar to that of methyl nitrococussate methyl ether (II; R = Me, Experimental).



VI

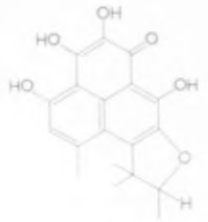


VII

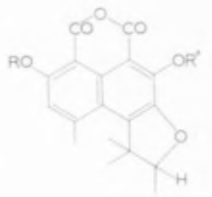


VIII

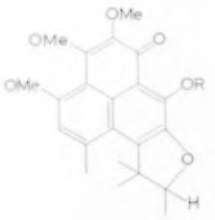
No evidence has yet been offered to distinguish between the alternative representations of the ether ring in (VIII). Thus in one formulation (VIII; R = Me; R′ = R″ = H) there is a hydrogen on the carbon atom to which the ethereal oxygen is attached, whilst in the other (VIII; R = R″ = H; R′ = Me) there is not. Dr. L. M. Jackman, to whom we express our best thanks, very kindly determined and interpreted the NMR spectrum of the phenol (VIII) in saturated pyridine solution (for calibration etc. see Experimental). There were signals at 1222 and 1218 (*gem.*-dimethyl) and 1134 (aromatic methyl) c.p.s. In addition there was a doublet (J = 6·5 c.p.s) at 1209 and a weak quartet (J = 6·5 c.p.s) at 1066 c.p.s. The 1066 c.p.s. signal is attributed to the proton (R′) attached to the same carbon atom as an oxygen atom and the doublet to the methyl group attached to this same carbon atom. The signal given by the proton is in accord with the structure (VIII; R = Me; R′ = R″ = H), its resonance frequency being close to the equivalent proton (1068) in *iso*propyl acetate.[14] Similarly the doublet at 1209 is close to the signal (1212 c.p.s.) for the methyl group of the ethyl residue of ethylacetate.[14] This evidence establishes the correctness of the formulation (VIII; R = Me; R′ = R″ = H).



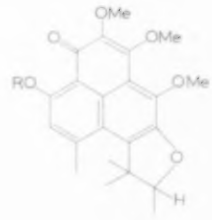
IX



X



XI



XII

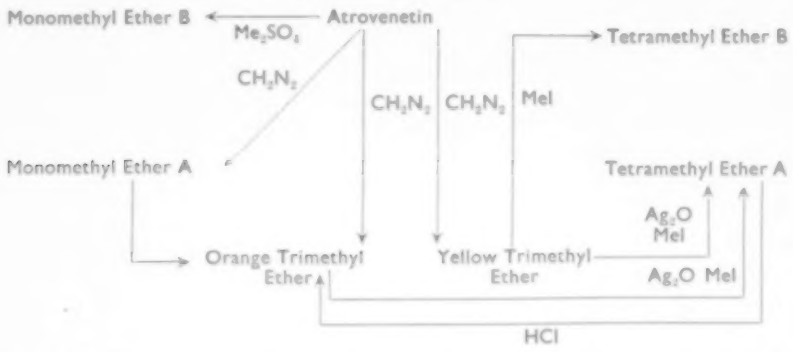
From these facts a unique structure for atrovenetin (IX or, of course, an equivalent tautomer) necessarily follows. The constitution (IX) accounts also for certain additional observations. By zinc dust distillation of atrovenetin Neill and Raistrick[1] obtained, in small yield, pyrene. On the basis of (IX) this is simply interpreted as cleavage of the ether followed by cyclisation onto the *peri*-position. The loss of methyl groups necessarily involved finds analogy in the chemistry of terramycin.[15]

With the structure of atrovenetin established it is now possible to discuss the

[14] A. A. Bothner-By, C. Naar-Colin and B. L. Shapiro, *NMR Spectra and Structure Correlations* Vol. II. Harvard Chemistry Department.

[15] F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *J. Amer. Chem. Soc.* **75**, 5455 (1953).

nature of certain of its transformation products. By the application of a number of methylation techniques Neill and Raistrick[1] prepared a large number of methyl ethers, the various interconversions being summarised below.

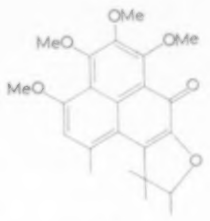


The nature of the trimethyl ethers has now been clarified by examination of their oxidation products. It has already been mentioned that chromic acid oxidation of the 'yellow' and 'orange' ethers gives two different anhydrides (IV; R or R′ = Me; R′ or R = H). In both of these one methoxyl group only is retained. It has now been found that nitric acid oxidation of the anhydride from the 'orange' trimethyl ether gives nitrococussic acid. This has been estimated by partition chromatography followed by spectroscopic analysis, and the substance responsible for the relevant band in the chromatogram has also been isolated as the crystalline acid and its identity confirmed. In contrast to this we were unable to isolate or detect any nitrococussic acid from the corresponding oxidation of the anhydride from the 'yellow' trimethyl ether. It thus follows that the anhydride from the 'orange' trimethyl ether is that in which the methoxyl group is *not* attached to the ring bearing the methyl group, and is therefore to be represented as (X; R = H; R′ = Me). The other anhydride then becomes (X; R = Me; R′ = H). Since, in the trimethyl ethers from which the anhydrides are derived, it must be presumed that the unmethylated hydroxyl group and the carbonyl group form a *peri*-hydrogen-bonded pair the yellow and orange trimethyl-ethers may be represented as (XI; R = H) and (XIII; R = H) respectively (or equivalent tautomers). Since tetramethyl ether B is derived from (XI; R = H), it seems probable that either (XI; R = Me) or (XIII) should represent this substance and similarly (XII; R = Me) or (XIV) must represent tetramethyl ether A. This is in accord with the hydrolysis of tetramethyl ether A back to the 'orange' trimethyl ether. Of these (XIV) must be correct because chromic acid oxidation of tetramethyl ether A gave the anhydride (X; R = H; R′ = Me), obtained from the 'orange' trimethyl ether. It was not, however, possible to distinguish between (XI; R = Me) and (XIII) in this way. The anomalous formation of *both* tetramethyl ethers from the yellow trimethyl ether requires the facile hydrolysis of one methoxyl group. This may be readily rationalised as an addition-elimination process, the hydrolysis taking place at a position β- or vinylogously β- to the carbonyl group.[16]

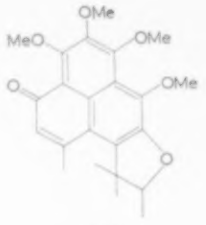
By the lithium aluminium hydride reduction of the trimethyl ethers of atrovenetin two isomeric substances, $C_{22}H_{24}O_5$, were obtained.[1] Since these both have the original

[16] Compare J. F. Grove, J. MacMillan, T. P. C. Mulholland and M. A. T. Rogers, *J. Chem. Soc.* 3949 (1952); A. E. Oxford, H. Raistrick and P. Simonart, *Biochem. J.* **33**, 240 (1939).

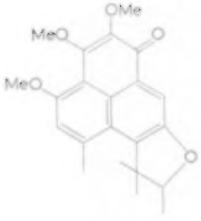
three methoxyl groups the reaction must be interpreted as a hydrogenolysis induced by 1:2- or 1:4-hydride addition followed by β-elimination. In confirmation of this both substances showed carbonyl bands (Table 1) indicative of a perinaphthenone. It follows that (XVa) or (XVb) and (XVIa) or (XVIb) may be written for the hydride



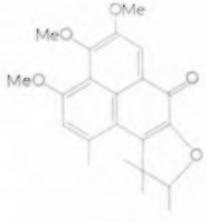
XIII



XIV



XVa



XVb

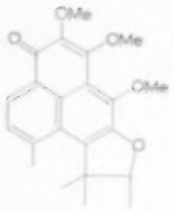
products derived from the 'yellow' and 'orange' trimethyl ethers respectively, but the available evidence does not permit a decision between the various structures.

Since deoxyherqueinone gives the anhydride (IV; R = R′ = H), now to be represented as (X; R = R′ = H), on oxidation, with loss of the methoxyl group it follows that in this substance, and, therefore, in herqueinone itself, the methoxyl group must be situated in ring C. In addition methylation of deoxyherqueinone with a solution of diazomethane in methylene dichloride has been found to give atrovenetin 'orange' trimethyl ether (XII; R = H) whence it follows that deoxyherqueinone must be represented by (XVII; R = H; R′ = Me) or by (XVII; R = Me, R′ = H). Deoxyherqueinone is not identical with either of the atrovenetin monomethyl ethers.

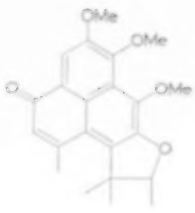
The biogenesis of atrovenetin calls for some comment. The nucleus, as found in xanthoherquein, appears to be based on the same poly-β-diketone system as has been postulated for the genesis of the naturally occurring anthraquinones,[17] and related *m*-hydroxylated aromatic substances. The manner in which the coiling of the poly-β-diketone chain is envisaged is indicated in (XVIII). The ethereal side chain of atrovenetin is also very unusual and requires comment. Of aromatic natural products of established constitution,[18] containing an isoprene side chain the overwhelming majority have this unit attached to the aromatic nucleus by the terminal (C_1) carbon

[17] *Inter al.* Sir R. Robinson, *Structural Relations of Natural Products.* Clarendon Press (1955); A. J. Birch and F. W. Donovan, *Aust. J. Chem.* **6**, 361 (1953).
[18] W. Karrer, *Konstitution und Vorkommen der Organischen Pflanzenstoffe.* Birkhauser Verlag, Basel (1958).

atom; that is through the carbon atom bearing the primary hydroxyl in a mevalonic acid precursor. These side chains also frequently contain an allylic double bond or its oxygenated equivalent. It is thus probable that these units are formed by elimination of the tertiary hydroxyl group of a mevalonic acid precursor followed by a

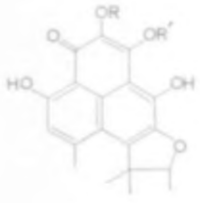


XVIa



XVIb

XVIII



XVII

XIX

XX

substitution process on the primary hydroxyl carbon. An intermediate such as (XIX or equivalent) may therefore be involved. The ether bridge in atrovenetin and that in dunnione[19] may thus be formed from the alternative coupling site in the mesomeric cation (XX) obtainable from (XIX).

We report briefly in the Experimental section the preparation of monobromo-derivatives of xanthoherquein, atrovenetin, herqueinone and *iso*herqueinone. The formation of such mono-derivatives from xanthoherquein and atrovenetin is, of course, to be expected since one free aromatic position *ortho* to a phenolic hydroxyl is available in both compounds. The studies now reported on atrovenetin have considerable bearing on the structure of herqueinone. We defer, however, any speculation pending the completion of experiments which are now in hand.

EXPERIMENTAL

$[\alpha]_D$ are in $CHCl_3$, ultra-violet absorption spectra refer to EtOH solution. Infra-red spectra were kindly determined by Dr. G. Eglinton and his colleagues (Glasgow). Microanalyses are by Mr. J. M. L. Cameron (Glasgow) and Miss J. Cuckney (Imperial College) and their colleagues. M.ps. were determined on the Köfler block unless otherwise stated. The term light petroleum refers to the fraction of b.p. 60–80°. The NMR spectra were determined on a Varian nuclear resonance spectrometer using a 40 Mc oscillator. The spectra were calibrated against *cyclo*hexane as an internal standard using the usual side band technique. *cyclo*Hexane at infinite dilution in CCl_4 gives a single line at 1204 c.p.s. relative to external toluene, the aromatic line of the latter being given the arbitary value of 1000 c.p.s.

[19] J. R. Price and Sir R. Robinson, *J. Chem. Soc.* 1523 (1939); 1493 (1940); R. G. Cooke, *Aust. J. Sci. Res.* **3A**, 481 (1950).

Bromoherqueinone

Herqueinone (50 mg) in acetic acid (100 ml) was treated with a solution of bromine in the same solvent (1·03 N; 1 ml). Titration of an aliquot indicated the uptake of 0·97 mole bromine in 10 min, no further uptake occurring over a further hour. Isolation of the product in the usual way gave, after crystallisation from chloroform—light petroleum *bromoherqueinone*, m.p. 235° (decomp), $[\alpha]_D$ +460° (*c* 0·054), $\lambda\lambda_{max}$ 222, 254–57, 266, 322–323, 410–414 mμ (log ε 4·49, 4·25, 4·27, 4·53, 3·72 respectively) (Found: C, 52·95; H, 4·55; Br, 17·5; OMe, 6·5; C—Me, 7·35; $C_{20}H_{19}O_7Br$ requires: C, 53·25; H, 4·25; Br, 17·7; OMe, 6·9; 2C—Me 6·65%).

Bromoisoherqueinone

A solution of bromine in acetic acid (0·88 N; 1 ml) was added to *iso*herqueinone (102 mg) dissolved in acetic acid (40 ml). The titration of aliquots indicated the uptake of 0·95 mole bromine. The red needles separating from the reaction medium were collected and crystallised from chloroform-light petroleum to give *bromoisoherqueinone*, decomposing slowly from 240° to 260° (capillary), $[\alpha]_D$ 0° (*c* 0·98). (Found: C, 53·35; H, 4·55; Br, 18·1. $C_{20}H_{19}O_7Br$ requires: C, 53·25; H, 4·25; Br, 17·7%). The infrared spectrum showed small differences from that of bromoherqueinone in the fingerprint region.

Bromoxanthoherquein

Xanthoherquein (53 mg) in acetic acid (100 ml) was treated with a solution of bromine in acetic acid (1.0 N; 1 ml). The titration of aliquots indicated the cessation of uptake after the consumption of 1·3 moles bromine. Isolation of the product in the usual way, followed by crystallisation from acetic acid, gave bright yellow needles of *bromoxanthoherquein*, decomposing slowly above 200°, $\lambda\lambda_{max}$ 220 and 426–429 mμ (log ε 4·64 and 4·23 respectively) (Found: C, 46·8; H, 3·05; Br, 20·65. $C_{15}H_{11}O_7Br$ requires: C, 47·05; H, 2·9; Br, 20·85%).

Bromoatrovenetin

Atrovenetin (51 mg) in acetic acid (50 ml) was treated with a solution of bromine in acetic acid (0·1 N, 5 ml). The titration of aliquots indicated that uptake of bromine ceased after 40 min with the consumption of 1 mole. On being set aside overnight the product crystallised from the solution to give, after crystallisation from acetic acid, *bromoatrovenetin*, m.p. 232–5°. (Found: C, 54·45; H, 4·35; Br, 19·4. $C_{19}H_{17}O_6Br$ requires: C, 54·15; H, 4·05; Br, 18·9%).

Deoxyherqueinone diacetate

(a) Herqueinone (520 mg) in acetic acid (125 ml) was shaken with zinc dust (5 gm) in a nitrogen atmosphere for 20 min. After filtration the acetic acid was removed *in vacuo* and the residue acetylated in the usual way (acetic anhydride-pyridine) to give, after crystallisation from methanol, *deoxyherqueinone diacetate*, m.p. 174–175°, $[\alpha]_D$ +57° (*c* 0·46). (Found: C, 65·25; H, 5·65; Ac, 20·2; $C_{21}H_{24}O_8$ requires: C, 65·45; H, 5·5; 2Ac, 19·5%).

(b) *iso*Herqueinone (110 mg) in acetic acid (25 ml) was shaken with zinc dust (1.0 g) under nitrogen for 20 min. Treatment of the product as described under section (a) gave deoxyherqueinone diacetate (m.p. and mixed m.p.).

Deoxynorherqueinone triacetate (*Atrovenetin triacetate*)

*nor*Herqueinone (354 mg) in pyridine (12 ml) and acetic acid (30 ml) was shaken with zinc dust (3 g) for 30 min. The reaction mixture was poured into water and the product isolated with chloroform. The amorphous residue remaining after removal of the solvent was a complex containing nitrogen. This was washed with acetone and used without further purification for acetylation. The deoxy*nor*herqueinone complex (298 mg) was set aside overnight with pyridine (2 ml) and acetic anhydride (4 ml), slow dissolution occurring. Isolation of the product in the usual way gave deoxy*nor*-herqueinone triacetate; m.p. 185–187° (from methanol), $[\alpha]_D$ +70° (*c* 0·57). (Found: C, 63·75; H, 5·4; Ac, 27·4. Calc. for $C_{25}H_{24}O_9$: C, 64·1; H, 5·15; 3Ac, 27·55%). The m.p. of the compound was undepressed on admixture with atrovenetin triacetate m.p. 185–7°, $[\alpha]_D$ +73° (*c* 0·70). The ultra-violet spectra (Table 2) were superposable as were the infra-red spectra both in nujol and chloroform. Powder diffraction photographs were kindly taken by Dr. J. C. Speakman (Glasgow) using CuK α-radiation and a 9·0 cm diameter camera and confirmed this identity.

Nitric acid oxidation of xanthoherquein

(a) Xanthoherquein (120 mg) and conc nitric acid (5 ml) were heated together on the steam bath for one hour. The mixture was then poured into water and the product isolated with ether. After removal of the solvent the residue was filtered in ether-benzene solution (1:9) through a short column (3 g) of silica. Crystallisation from benzene-light petroleum gave nitrococussic acid (II; R = H)[7,8] m.p. 179–180° (evacuated capillary), λ_{max} 380–383 mμ (log ε 3·9) (Found: C, 33·2; H, 2·0; N, 14·3. Calc. for $C_8H_5N_3O_9$: C, 33·45; H, 1·75; N, 14·65%). The compound gave a yellow-brown colour with ferric chloride and showed bands at 3480 and 1720 cm^{-1} in the infra-red spectrum.

(b) Xanthoherquein (112 mg) was heated on the steam bath with conc nitric acid (5 ml) for 10 min. Isolation of the product as described under section (a) followed by methylation with excess ethereal diazomethane gave, after filtration in light petroleum solution through a short column (2 g) of alumina and crystallisation from aqueous methanol, *dimethyl nitrococussate*, (II; R = Me) m.p. 135–6°, λ_{max} 298–301 mμ (log ε 3·24) (cf VIII; R = R″ = Me, R′ = H, λ_{max} 309 mμ (log ε, 3·35)) (Found: C, 38·1; H, 3·3; N, 13·0; OMe, 19·25. $C_{10}H_9O_9N_3$ requires: C, 38·1; H, 2·9; N, 13·3; 2 (OMe) 19·8%). The material gave no colour with ferric chloride and showed a band in the infra-red spectrum at 1740 cm^{-1}. Decarboxylation of nitrococussic acid, as described by Liebermann and van Dorp,[8] gave 2:4:6-trinitro-*m*-cresol, m.p. 104–106°, undepressed on admixture with an authentic specimen of the same m.p.[20] The ultra-violet and infra-red spectra of the decarboxylation product and of the authentic 2:4:6-trinitro-*m*-cresol were superposable. Methylation of the decarboxylated product with excess ethereal diazomethane gave, after crystallisation from methanol, the methyl ether, m.p. 89–90°. (Found: N, 16·05. Calc. for $C_8H_7O_7N_3$: N, 16·35%). Preparation of the methyl ether of 2:4:6-trinitro-*m*-cresol gave material identical in every respect with the above-mentioned methyl ether.

Nitric acid oxidation of nor*xanthoherquein*

*nor*Xanthoherquein (235 mg) was heated on the steam bath for 70 min with conc nitric acid (10 ml). Isolation of the product in the manner described in the oxidation

[20] E. Reisz and F. Pilpel, *Monatshefte* **50**, 335 (1928).

of xanthoherquein gave material, m.p. 180–181 (decomp, sealed capillary) undepressed on admixture with nitrococussic acid. Methylation with ethereal diazomethane gave material m.p. 134–5°, undepressed on admixture with the methylation product of nitrococussic acid.

The anhydride (X; R = R′ = H)

(a) Atrovenetin (100 mg) was dissolved in boiling absolute alcohol (100 ml), the solution cooled to 0° and sodium hydroxide solution (4 N; 18 ml) added, followed rapidly by hydrogen peroxide (30%; 18 ml) and water (20 ml). After standing 5 min at 0° the excess peroxide was destroyed with platinum catalyst, and hydrochloric acid (6 N) added to adjust the pH to 3–4. The mixture was then diluted with saturated ammonium chloride solution and repeatedly extracted with ether. Evaporation of the ether gave a red oily residue. This was applied to a cellulose[21] column (35 cm × 4 cm) in, and eluted with, the upper layer of the system obtained from *n*-butanol, benzene and aqueous ammonium carbonate and hydroxide, 1·5 N with respect to each (1 : 49 : 50). The zone which fluoresced blue under ultra-violet light was collected, and after removal of the solvent the residue was crystallized from benzene-light petroleum and chloroform-light petroleum to give the *anhydride* (X; R = R′ = H), m.p. 255–256°, $[\alpha]_D$ + 76°(*c* 0·17), $\lambda\lambda_{max}$ 256, 297–298, 360–361 mμ (log ε 4·47, 3·94, 4·12 respectively) (Found: C, 65·9; H, 5·0; $C_{18}H_{16}O_6$ requires: C, 65·85; H, 4·9%). The compound did not react with sodium hydrogen carbonate but gave a deep brown-red colour with ethanolic ferric chloride. A negative result was obtained in the Thomas catechol test.[22] Solutions of the compound gave a bright blue fluorescence under ultra-violet light. Acetylation of the compound (acetic anhydride-pyridine) gave, after isolation and crystallisation from ethyl acetate-light petroleum, the *diacetate* (X; R = R′ = Ac), m.p. 176–181°, $\lambda\lambda_{max}$ 264 and 377–378 mμ (log ε 4·59 and 4·07 respectively) (Found: C, 64·35; H, 4·85; Ac, 20·6; $C_{22}H_{20}O_8$ requires: C, 64·05; H, 4·9; 2Ac, 20·85%).

(b) Herqueinone (292 mg) was dissolved in pyridine (5 ml) and acetic acid (25 ml) and after the addition of zinc dust (3 g) the mixture was shaken for 20 min. The zinc was then removed by filtration, the mixture acidified with 6 N sulphuric acid and the precipitated zinc salts filtered off. The filtrate was heated on the steam bath, and a solution of chromic acid (590 mg) in aqueous acetic acid (85%; 23 ml) added dropwise over 30 min. Heating was continued over 1½ hr. After working up in the usual way the product was chromatographed on silica, followed by crystallisation from chloroform–light petroleum, to give the anhydride (X; R = R′ = H), m.p. and m.m.p. 250–252°, $[\alpha]_D$ +72° (*c* 0·18). The ultra-violet and infra-red spectra were superposable.

(c) The anhydride (X; R = Me; R′ = H) (36 mg) was added to refluxing pyridine hydrochloride (1.0 g) and the heating continued for 4 min. The residue obtained after isolation in the usual way, followed by evaporation of the solvent, was dissolved in benzene and filtered through a short column of silica to give the anhydride (X; R = R′ = H), m.p. and m.m.p. 254–255°, $[\alpha]_D$ +73° (*c* 0·51). The identity was confirmed by the identical infra-red spectra of the two samples.

(d) The anhydride (X; R = H; R′ = Me) (31 mg) was demethylated as described for the anhydride (X; R = Me; R′ = H) under (c) to give, after crystallisation from chloroform–light petroleum, the anhydride (X; R = R′ = H), m.p. and mixed m.p.

[21] L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.* 2511 (1949).
[22] A. A. Thomas, *Chim. Anal.* **29**, 15 (1947).

255–256°, $[\alpha]_D$ +78° (*c* 0·56). The identity was confirmed by the superposability of the ultra-violet and infra-red spectra.

The anhydride (X; R = H; R′ = Me)

(a) Atrovenetin 'orange' trimethyl ether (510 mg) was dissolved in acetic acid (3 ml) at 100°. Chromium trioxide (572 mg) in aqueous acetic acid (85%; 23 ml) was added dropwise and the heating continued for 2 hr after the addition. After isolation in the usual way the product was added in benzene solution to a column of silica (30 g). Elution with ether-benzene (1 : 99) gave, after crystallisation from chloroform-light petroleum, the *anhydride* (X; R = H; R′ = Me), m.p. 235–236°, $[\alpha]_D$ +75° (*c* 0·58). [The mixed m.p. with the anhydride (X; R = Me; R′ = H) was 212°], $\lambda\lambda_{max}$ 233, 258, 341, 370 and 386 mμ (log ε, 4·26, 4·51, 4·07, 4·11 and 4·07 respectively) (Found: C, 66·5; H, 5·5; OMe, 9·15; $C_{19}H_{18}O_6$ requires: C, 66·65; H, 5·3; 1 OMe, 9·05%).

(b) Atrovenetin tetramethyl ether A (99 mg) was dissolved in acetic acid (2 ml) at 100°, and chromium trioxide (110 mg) in aqueous acetic acid (85%; 6 ml) added dropwise. Heating was continued for 2 hr. Isolation of the product as described under (a) gave, after crystallisation from chloroform-light petroleum, the anhydride (X; R = H; R′ = Me), identical in every respect with that obtained by oxidation of the 'orange' trimethyl ether.

Nitric acid oxidation of atrovenetin

Atrovenetin (103 mg) was heated on the steam bath for 2 hr with conc nitric acid (5 ml). Isolation of the product in the usual way gave an oil which was methylated with excess ethereal diazomethane and the methylated derivative, in benzene-light petroleum solution (7 : 3), filtered through a short column of alumina. Re-chromatography on alumina gave methyl nitrococussate, m.p. and m.m.p. 133–135°.

Nitric acid oxidation of the anhydrides (X; R = Me; R′ = H) *and* (X; R = H; R′ = Me)

(a) The anhydride (X; R = Me; R′ = H) and the anhydride (X; R = H; R′ = Me) (20·8 mg) were each heated for 1 hr with conc nitric acid (1 ml) on the steam bath. After isolation of the products in the usual way, the yellow gums so obtained were examined by ascending partition chromatography using the upper layer of the system *n*-butanol-acetic acid-water (4 : 1 : 5). The section of the strips in the region R_F 0·4 (that of nitrococussic acid) was cut into strips and eluted with boiling ethanol. With an appropriate blank, and using the optical density at 380 mμ it was found that the anhydride (X; R = H; R′ = Me) gave >200 times as much nitrococussic acid as did the anhydride (X; R = Me; R′ = H).

(b) The anhydride (X; R = H; R′ = Me) (123 mg) was heated on the steam bath with conc nitric acid (6 ml) for 1 hr. The gum obtained by isolation in the usual way was added in *iso*-propanol-ammonia (0·15 N) (4 : 1) to a column of cellulose powder (21 cm × 2·5 cm) previously washed with ethanol and with *iso*propanol-ammonia. The crystalline fractions were combined and recrystallised from chloroform-light petroleum to give nitrococussic acid, identified by m.p., mixed m.p., ultra-violet and infra-red spectra.

(c) The anhydride (X; R = Me; R′ = H) (160 mg) was oxidised on the steam bath in conc nitric acid (5 ml) for 1 hr. Isolation of the product gave a gum which

crystallised on titration with methanol. Crystallisation from chloroform-light petroleum gave a *compound*, m.p. 215–225° (gas evolution), $[\alpha]_D$ +161° (*c* 0·29), $\lambda\lambda_{max}$ 231 and 321 mμ (log ε, 4·50 and 3·74 respectively). (Found: C, 52·9; H, 4·45; N, 3·3; OMe, 7·2; $C_{18}H_{17}O_{10}N$ requires: C, 53·05; H, 4·2; N, 3·45; 1 OMe, 7·6%).

Base treatment of the phthalide (VIII; R = Me; R′ = R″ = H)

The phthalide (VIII; R = Me; R′ = R″ = H) (104 mg) in ethanol (5 ml) was added to water (5 ml) containing sodium hydroxide solution (4 N; 30 drops). After 10 min the solution was acidified (hydrochloric acid) and the product isolated with ether. The yellow gum obtained on evaporation of the ether was methylated, in ethyl acetate solution, with excess ethereal diazomethane. Evaporation and crystallisation from dry ether gave the *methyl ester methyl ether*, m.p. 125–130°, $[\alpha]_D$ −89° (*c* 1·08), λ_{max} 295 mμ (log ε 3·23) (Found: C, 49·75, H, 5·0; N, 6·65; OMe, 15·05; $C_{17}H_{20}O_{10}N_2$ requires: C, 49·5; H, 4·9; N, 6·8; 2 OMe, 15·05%).

2:7-*Dimethoxynaphthalic anhydride* (V; R = Me)

3:8-Dimethoxyacenaphthene quinone[23] (504 mg) was dissolved in ethanol (3 ml) and sodium hydroxide solution (4 N; 25 ml), hydrogen peroxide (30%; 25 ml) and water (35 ml) added. After standing 30 min the solution was acidified and the crystalline precipitate collected. Crystallisation from ethylene glycol then gave 2:7-*dimethoxynaphthalic anhydride* (V; R = Me), m.p. 340–344°, $\lambda\lambda_{max}$ 245, 283 and 365 mμ (log ε, 4·58, 3·65 and 4·26 respectively) (Found: C, 65·05; H, 4·05; OMe, 23·9. $C_{14}H_{10}O_5$ requires: C, 65·1; H, 3·9; 2 OMe, 24·05%).

2:7-*Dihydroxynaphthalic anhydride* (V; R = H)

2:7-Dimethoxynaphthalic anhydride (40 mg) was added to refluxing pyridine hydrochloride (1·2 g) and the heating continued for a further 3 min. The product was isolated in the usual way and crystallised from chloroform-light petroleum to give 2:7-*dihydroxynaphthalic anhydride* (V; R = H), m.p. 283–284°, $\lambda\lambda_{max}$ 225, 240, 285, 335, 355, and 365 mμ (log ε 4·39, 4·39, 3·73, 3·97, 4·03 and 4·09 respectively) (Found: C, 62·4; H, 2·85. $C_{12}H_6O_5$ requires: C, 62·6; H, 2·65%). The anhydride (37 mg) on acetylation (acetic anhydride-pyridine) gave, in the usual way, after crystallisation from chloroform-light petroleum, the *diacetate* (V; R = Ac) m.p. 265–269° (sealed capillary) $\lambda\lambda_{max}$ 238, 330 and 343 (log ε, 4·64, 4·09 and 4·11 respectively) (Found: C, 60·85; H, 3·4. $C_{16}H_{10}O_7$ requires: C, 61·15; H, 3·2).

Dimethyl 2:7-*dimethoxynaphthalate*

2:7-Dimethoxynaphthalic anhydride (55 mg) was dissolved in aqueous sodium hydroxide (4 N; 1·5 ml) and water (9·5 ml). The solution was acidified at 0° and the precipitate collected immediately. The wet precipitate was suspended in methylene dichloride and methylated with ethereal diazomethane. Isolation of the product and crystallisation from chloroform-light petroleum gave *dimethyl* 2:7-*dimethoxynaphthalate*, m.p. 128–130°, $\lambda\lambda_{max}$ 239, 308–13, 320, and 334 mμ (log ε, 4·79, 3·74, 3·74, 3·74 respectively) (Found: C, 62·75; H, 5·05; OMe, 40·7; $C_{16}H_{16}O_6$ requires: C, 63·15; H, 5·3; (4) OMe, 40·8%).

[23] H. Staudinger, H. Goldstein, and E. Schlenker, *Helv. Chim. Acta* **4**, 342 (1921).

Methylation of deoxyherqueinone

Deoxyherqueinone (153 mg) was treated in methylene dichloride with an excess of diazomethane in methylene dichloride solution and set aside for 20 hr. The red oil obtained on evaporation of the solvent was chromatographed on silica to give, after crystallisation from chloroform-light petroleum, atrovenetin orange trimethyl ether, m.p. 176–179°, identical in all respects with an authentic specimen. The m.p. was depressed to 135° on admixture with the yellow trimethyl ether (m.p. 163–169°).

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STUDIES ON ARGENTINE PLANTS—XVII*

THE STRUCTURE OF FAGARINE II

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Abstract—The structure of fagarine II, an alkaloid from *Fagara coco* (Gill.) Engl., has been elucidated through its transformation into tetra-hydro-pseudo berberine.

IN common with other species of the *Rutaceae* family, a number of alkaloids belonging to different chemical types have been isolated from *Fagara coco* (Gill.) Engl.[1] In leaves and twigs, the furoquinoline bases γ-fagarine and skimmianine and the protopine alkaloids *allo*cryptopine (α-fagarine) and fagarine II, have been found.[1–3] From the bark, besides skimmianine and *allo*cryptopine,[4] an aporphine alkaloid, N-methyl-*iso*corydine, has also been isolated.[5] Fagarine III, a minor alkaloid of unknown structure, was found in the extracts from leaves and twigs.[3]

Fagarine II, according to the information given by Stuckert,[1] was first isolated in Merck's Laboratories in Darmstadt. Later, Redemann, Wisegarver and Alles,[3] again obtained the same base.

They suggested that fagarine II was a member of the protopine alkaloids, because its ultraviolet spectrum was very similar to that of *allo*cryptopine, and on treatment with phosphoryl chloride, it gave an anhydromethochloride, a reaction that is considered typical of that group of bases. The same workers showed that it was isomeric with *allo*cryptopine, both having two methoxy- and one methylenedioxy-group. The difference between the bases should then be only one of the location of the substituents.

The experiments reported here show that fagarine II has structure (I). The possibility that fagarine II should have this structure, or the isomeric one (II), was suggested from a comparison of its infrared spectrum (Fig. 1) with that of *allo*-cryptopine (Fig. 2). Both spectra have a certain similarity. However, in the region of out of plane aromatic carbon–hydrogen deformation vibrations, the spectrum of *allo*cryptopine has a strong band at 812 cm^{-1}, a region that has been assigned to two vicinal hydrogen atoms (800–860 cm^{-1}), and the band should arise from the two *ortho* hydrogen atoms present in ring D of the base; this band is totally absent in the spectrum of fagarine II, that should not have *ortho* hydrogen atoms in neither of the aromatic rings A and D. Another difference is found in the region of 855–870 cm^{-1},

* Part XVI: M. J. Vernengo, A. S. Cerezo, G. Iacobucci and V. Deulofeu, *Liebigs Ann.* **610**, 173 (1957); *Anal. Asoc. Quim. Arg.* **46**, 149 (1958).

[1] G. V. Stuckert, *Investigaciones del Laboratorio de Química Biológica*, p. 109, Vol. I, Córdoba, Argentina (1933); V. Deulofeu and J. Comín, *Il Farmaco* **9**, 340 (1954).
[2] V. Deulofeu, R. Labriola and J. De Langhe, *J. Amer. Chem. Soc.* **64**, 2326 (1942).
[3] C. E. Redemann, B. B. Wisegarver and G. A. Alles, *J. Amer. Chem. Soc.* **71**, 1030 (1949).
[4] E. M. Barilari and J. Comín, *Anal. Asoc. Quím. Arg.* **43**, 180 (1955).
[5] J. Comín and V. Deulofeu, *J. Org. Chem.* **19**, 1774 (1954); *Anal. Asoc. Quím. Arg.* **43**, 83 (1955).

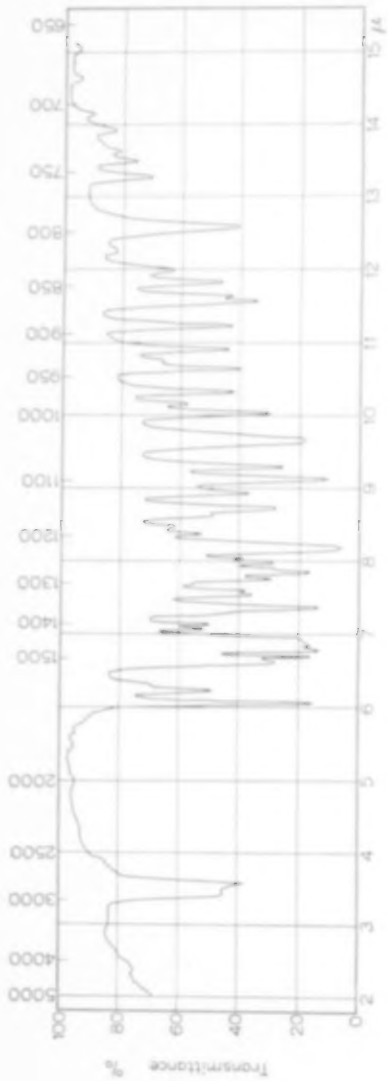


Fig. 1. IR-spectrum of fagarine II (Nujol)

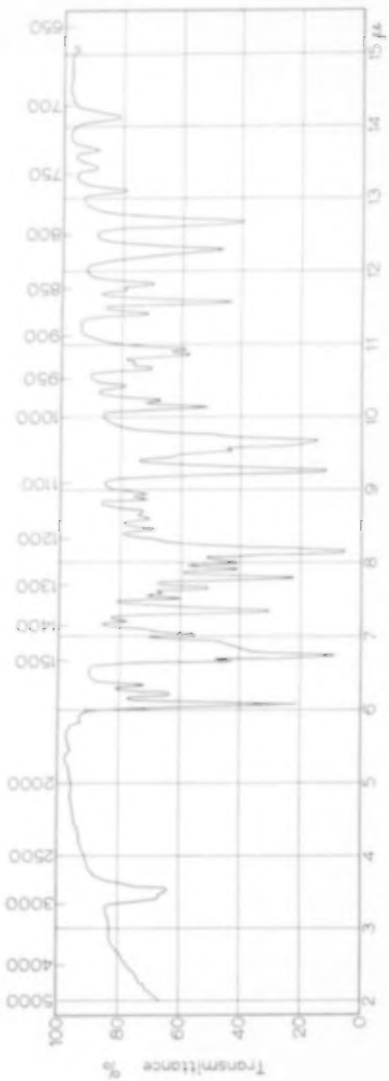
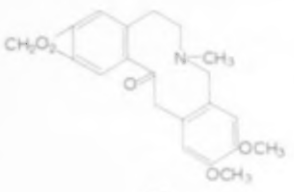


Fig. 2. IR-spectrum of allocryptopine (Nujol)

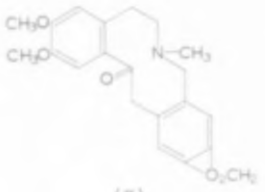
assigned to 1:2:4:5-tetra substituted benzene derivatives.[6,7] The spectrum of *allo*-cryptopine presents a band at 866 cm^{-1} that should originate in the vibration of the two *para* hydrogens atoms of ring A, a band that is stronger in the spectrum of fagarine II (864 cm^{-1}). A little displaced from the assigned region, another band is found at 846 cm^{-1}, which is also stronger in fagarine II than in *allo*cryptopine. The higher absorption in those bands in the case of fagarine II, was interpreted as showing that rings A and D have in this base two hydrogen atoms in *para* position (structure I or II).

To decide on the two alternatives, fagarine II was transformed into the tetrahydro berberine base, by applying the method developed by Späth and Posega,[7] in the synthesis of coptisine from protopine.

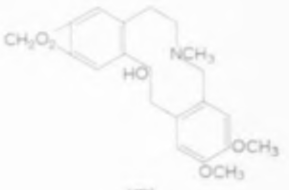
Fagarine II was reduced to the carbinol base (III) with sodium amalgam, the reduced alkaloid dehydrated and cyclized by evaporation to dryness of its slightly acidic solution and the quaternary base (IV) separated as the iodide. The quaternary iodide by high vacuum sublimation yielded a product that was identified by its infrared spectrum and mixed melting point as tetrahydro-pseudoberberine (V), synthesized already by Haworth, Perkin and Rankin.[8] The two methoxy-groups of fagarine II are located in carbons 10 and 11 instead of carbons 9 and 10, the usual position of substituents in the natural protopine and protoberberine groups of bases. Fagarine II has the substituents in the same places as coreximine,[9] a base that stood alone in this respect and Robinson had remarked[10] that it was an exception to the usual places of substitution in the protopine, berberine, phtalide-*iso*quinoline and α-naphthaphenanthridine groups of alkaloids.



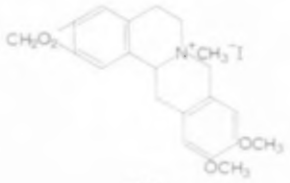
(I)



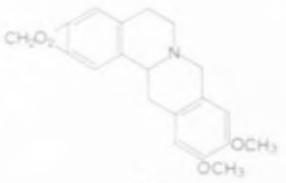
(II)



(III)



(IV)



(V)

Another point is the position of the hydrogen atom in carbon 14 of tetrahydro-pseudoberberine. The *trans*(α, *normal* or *allo*) position to the lone pair of electrons

[6] L. J Bellamy, *The Infra-red Spectra of Complex Molecules*, p. 67. Methuen, London (1954); R. Norman Jones and C. Sandorfy, *Technique of Organic Chemistry* (Edited by W. West) p. 387, Vol. IX, Interscience, New York (1956).
[7] E. Späth and R. Posega, *Ber.* **62,** 1029 (1929).
[8] R. D. Haworth, W. H. Perkin and J. Rankin, *J. Chem. Soc.* 1686 (1924).
[9] R. H. F. Manske, *Canad. J. Res.* **16B,** 81 (1938); *J. Amer. Chem. Soc.* **72,** 4796 (1950).
[10] R. Robinson, *The Structural Relations of Natural Products* p. 86, Oxford Univ. Press (1955).

of the nitrogen atoms, when the carbon hydrogen bond is axial to both rings B and C, must be the most stable and that which will be formed in a preferential way in the transformation of the carbinol base (III) to tetrahydro-pseudoberberine (V). This is in agreement with the infrared spectrum of the last base in the region 2700 to 3000 cm^{-1}.

As Bohlmann and co-workers[11] have pointed out for the *Lupinus* alkaloids and Wenkert and Roychaudhuri[12] for some indole alkaloids, certain neat peaks are observed in the bands around 2800 cm^{-1} in substances with a quinazolidine structure,

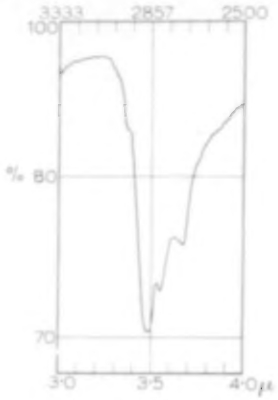
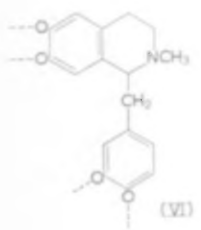


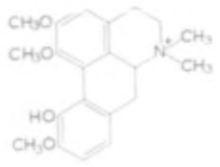
FIG. 3.

when the union of the two quinazolidine rings is *trans*. In the case of tetrahydro-pseudoberberine those peaks are present as shown in Fig. 3. It follows that it must have in carbon-14 an axial hydrogen atom to rings B and C with a *trans* union of the quinazolidine rings.

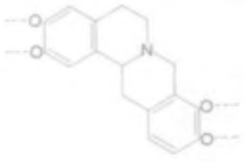
The genesis of three of the alkaloids that have been isolated from *Fagara coco*,



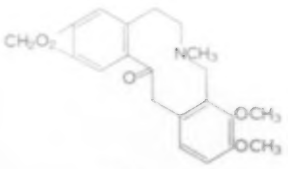
(VI)



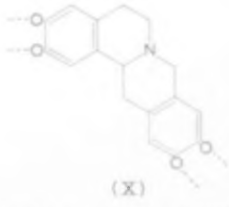
(VII)



(VIII)



(IX)



(X)

[11] F. Bohlmann, W. Weise, H. Sander, H. Hanke and E. Winterfeldt, *Chem. Ber.* **90**, 653 (1957).
[12] E. Wenkert and D. K. Roychaudhuri, *J. Amer. Chem. Soc.* **78**, 6417 (1956).

can be explained by a common four substituted benzyl-*iso*quinoline, precursor (VI). Condensation by dehydrogenation can give rise to an aporphine base with the substituents in the places found in N-methyl *iso*corydine (VII). Condensation with a one carbon unit in *ortho* position to a substituent, produces a protoberberine (VIII) that by oxidation can give rise to *allo*cryptopine (IX). If the condensation takes place in *para* to the same substituent, a tetrahydro-pseudoberberine (X) is produced, that should be the precursor of fagarine II (I). This last type of condensation, that took place in the laboratory, in the synthesis of tetrahydro-pseudoberberine,[8] is represented also in nature by the formation of coreximine.

VOL. 6 1959

EXPERIMENTAL

Melting points are uncorrected.

Tetrahydro-pseudoberberine (V) *from fagarine* II (I). Fagarine II, m.p. 195–196° (1 g) was dissolved in 1 N H_2SO_4 (200 ml), 5% sodium amalgam (200 g) added and the mixture heated in a water bath, with stirring, for 2 hr, when the evolution of hydrogen has practically ceased. In order to keep the solution acid, 2 N H_2SO_4 was added from time to time during the operation, in total 125 ml.

The solution, separated from the mercury, was filtered, made slightly alkaline with solid sodium hydrogen carbonate and again faint acid with 2 N HCl. This acid solution was evaporated to dryness, in the water bath at atmospheric pressure, and heated further for 1 hr. The residue was dissolved in water (300 ml), filtered from a small turbidity and the filtrate alkalinized with 2 N NaOH and extracted with ether to eliminate all the non-quaternary bases. The aqueous solution was neutralized with 2 N HCl, sodium thiosulfate (1 g) and sodium iodide (2 g) added, and stirred in the cold. The iodide of the quaternary base, *tetrahydro-pseudoberberine methiodide*, precipitates in crystalline condition and after standing overnight was filtered. 0·5 g were collected, m.p. 175–188°. Recrystallization from water increased the m.p. to 190–205°, but it was never sharp. The methiodide, undoubtedly a mixture, gave a correct value for iodine and was not further purified (Found: I, 25·81; Calc. for $C_{20}H_{21}NO_4 \cdot CH_3I$: 25·13%). The methiodide of tetrahydro-pseudoberberine prepared by Haworth, Perkin and Rankin,[8] m.p. 256°. The methiodide was decomposed by heating at 280° (bath temp) and 0·02 mm pressure.

A reddish sublimate was produced, (150 mg) and recrystallized from a small amount of methanol. After three crystallizations, needles melted at 175–176° were obtained. They gave no depression when mixed with an authentically original sample of tetrahydro-pseudoberberine m.p. 175–176°.

The infrared spectra of the two bases were also identical.

The *picrate* prepared from the sample deriving from fagarine II, melted at 174°. (Haworth, Robinson and Rankin give m.p. 176°.)

Acknowledgements—We thank Prof. R. D. Haworth for his kind gift of a sample of tetrahydro-pseudoberberine, Dr. N. H. Coy, The Squibb Institute for Medical Research, New Brunswick, New Jersey, for her help in recording the IR-spectra, and to Atanor S.A. for a grant.

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BOND LENGTHS AND BOND ENERGIES IN CONJUGATION AND HYPERCONJUGATION*

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(*Received* 21 *November* 1958)

Abstract—Dewar's arguments to the effect that all evidence for the existence of appreciable effects of π-electron resonance in the ground states of conjugated and hyperconjugated molecules is inconclusive, and that all observed effects are explainable as a result of differences in hybridization in carbon σ bond orbitals, are examined. It is shown that the C—C bond-length shortenings predicted by up-to-date π-electron theory are not as great as usually supposed, and that the corresponding predicted *lengthenings* of C=C and C≡C bonds are almost *nil*. It is concluded that Dewar is partly right in supposing that the lengths of conjugated and hyperconjugated C—C single bonds are determined, to a greater extent than previously supposed, by the states of hybridization of the carbon σ bond orbitals. However, there seems to be no justification for Dewar's assumption that resonance shortenings are negligible. Tentative formulas for the contributions of resonance and hybridization are given, also a similar formula for the shortening of conjugated or hyperconjugated C=C bonds in the cumulenes. Bond angles and hybridization are discussed, and the probable existence of marked deviations from ideal trigonal and digonal hybridization, often in opposite directions for C—H and C—C or C=C carbon σ orbitals, is emphasized. These differences may help to explain why C—H bonds are shortened less than C—C bonds involving supposedly similar hybrids.

Rather general bond energy formulas are given which assume additivity of bond energies but with a different bond energy for each hybrid type of C—H or C—C (or C=C) bond. It is shown that these reduce to the usual simple formula which ignores differences in hybrid type under not unplausible assumptions which, however, are at fault in neglecting polar energies (i.e. ionic-covalent resonance energies), especially in CH bonds. Dewar's assumption that CH bond energies are essentially independent of hybridization, and his consequent conclusion that observed stabilization energies in conjugated systems are due entirely to strengthened hybrid C—C bonds and not at all to π-electron resonance energy, is difficult to justify, especially in view of the expected importance of polar energies in CH bonds. A table of predicted polar energies for C—H and C—C bonds involving various hybrid C—C σ orbitals is given. The estimation of π-electron energy in C_2H_4, and of π-electron conjugation energy in butadiene, based on some energy data for 90° twisting, are discussed. Diphenyl and *s-cis* butadiene are compared.

The relative importance of π-electron resonance and hybridization in determining the dipole moments of conjugated and hyperconjugated molecules are discussed. While any conclusive theoretical calculation would in most cases be extremely complicated, there seems to be no good reason to doubt that π-electron resonance makes important contributions. Very strong evidence from nuclear magnetic resonance data is cited in support of usual current beliefs as to the role of π-electron resonance in charge distribution in conjugated and hyperconjugated molecules. Other evidence, including dipole moments in agreement with π-electron resonance theory predictions for molecules like fulvene and azulene where no differential hybridization effects should contribute, is cited.

INTRODUCTION

DEWAR and Schmeising[1] have argued that the physical evidence usually cited in proof of π-electron delocalization as the cause of ordinary (sacrificial) conjugation and hyperconjugation in ground states of unsaturated molecules is inconclusive; and have gone further in an effort to show that the effects of π-electron resonance are

* This work was assisted under a grant from the National Science Foundation.

[1] M. J. S. Dewar and A. N. Schmeising, Report at Conference on Hyperconjugation, Bloomington, Indiana, June, 1958. *Tetrahedron* **5**, 166 (1959).

negligible in these systems, and much smaller than usually believed even in systems involving isovalent conjugation, such as benzene or the allyl radical. (Burawoy[2] has long advocated the idea that there is no such thing as π-electron resonance).

Dewar cites the following types of evidence as inconclusive, for the reasons given:

(1) *Bond lengths.* Although conjugated and hyperconjugated C—C bonds are shortened (from 1·54 Å in C_2H_6 to 1·501 ± 0·002 in acetaldehyde, 1·48 ± 0·01 Å in butadiene,[3] 1·46 Å in CH_3—C≡CH, 1·38 Å in diacetylene, etc.) much more than (*about* 8/3 *as much as*) one would expect from observed C—H bond lengths with carbon atoms in supposedly corresponding states of hybridization (C—H lengths about 1·09 Å, 1·085 Å, and 1·06 Å in C_2H_6, C_2H_4, and C_2H_2 respectively), this can be accounted for by assuming that the shortening of the carbon atom covalent radius for trigonal or digonal hybridization is greater in C—C than in C—H bonds, so that π-electron resonance is not needed to explain the extra shortenings. (Hitherto,[4] it had been assumed that the shortening of the covalent radius of carbon, attributed to increased *s* character in the carbon bond orbital, is *the same* in C—C as in C—H bonds, and that a corresponding *part* of the C—C bond shortening observed in conjugation and hyperconjugation is due to this decrease in carbon orbital covalent radius.) Moreover, the lengths of such C—C bonds for a given hybrid type are remarkably constant (e.g. in H_3C—C≡CH, F_3C—C≡CH, Me_3C—C≡CH, H_3C—C≡N, etc.) Also, the lengths of C=C and C≡C bonds seem to be unaffected by ordinary conjugation or hyperconjugation. Finally, the trigonal-trigonal C—C bond in octatetraene is 1·46 Å although there can presumably be no appreciable π-electron delocalization since adjacent C=C bonds are twisted by 80°. (Further, there is convincing spectroscopic evidence that alternation of single and double bonds persists in, for example, the higher conjugated polyenes, without change from the lengths occurring in butadiene.[6]) Dewar concludes that the C—C lengths are completely explained by changes in covalent radius of carbon due to hybridization, and finds that the covalent radius is a "linear function of *s* character," meaning that the shortening from "sp^3" to "sp^2" carbon is equal to that from "sp^2" to "sp" carbon and so on.

(2) *Bond energies.* Although extra stabilities of conjugated and hyperconjugated systems, disclosed by energy or the like formulas based on addivity, are currently attributed to π-electron resonance stabilization, they can instead be consistently explained by assuming suitable increased strengths for C—C bonds whose bond orbitals are hybrids having more *s* character than in C_4H_6. However, the possibility of such an explanation depends on assuming that C—C bonds are strengthened *more* than C—H bonds by increased *s* character in the carbon bond orbitals; in fact Dewar assumes that C—H bonds are strengthened not at all (or negligibly), in for example C_2H_2 and C_2H_4 as compared with C_2H_6; he justifies this in terms of the conclusion reached in (1) that the carbon covalent radius is decreased much more in C—C bonds than in C—H bonds by increased *s* character in the bond orbital.

[2] A. Burawoy, *Chem. & Ind.* **51**, 434 (1944); *Trans. Faraday Soc.* **40**, 537 (1944); *V. Henri Memorial Volume*. Desoer, Liège (1948).
[3] O. Bastiansen, Private communication.
[4] L. Pauling, H. D. Springall and K. J. Palmer, *J. Amer. Chem. Soc.* **61**, 927 (1929); R. S. Mulliken, C. A. Rieke and W. G. Brown, *J. Amer. Chem. Soc.* **63**, 41 (1941); C. A. Coulson, *V. Henri Memorial Volume* p. 15. Desoer, Liège (1948).
[5] O. Bastiansen, L. Hedberg and K. Hedberg, *J. Chem. Phys.* **27**, 1311 (1957).
[6] J. R. Platt, *J. Chem. Phys.* **25**, 80 (1956); H. Krauch, *J. Chem. Phys.* **28**, 898 (1958); and references cited in these articles.

(3) *Dipole moments.* The existence of dipole moments in such molecules as propylene, toluene, and methylacetylene, usually attributed to hyperconjugation, can be fully explained by the fact that the C—C single bonds in these molecules involve orbitals differing in hybrid character, hence in electronegativity.

(4) *Electronic spectra.* Electronic spectra showing red shifts on methyl (or alkyl) substitution next to a multiple bond prove nothing about π-electron hyperconjugative delocalization in the *ground* state, since an excited state is also involved. They are of course consistent with real π-delocalization effects in the excited state.

(5) *Reaction rates.* Differences in reaction rates prove nothing about ground states, since they are likely to be due to peculiarities of transition states or reaction intermediates.

In a preceding paper,[7] the writer has pointed out the need to distinguish between ordinary (sacrifical) and isovalent conjugation and hyperconjugation, and the fact that relatively large effects are associated with isovalent hyperconjugation. The present paper, prepared in preliminary form in August and in final form in November, 1958, includes a considerable amount of further study carried out after the Conference. In it, Dewar's views as summarized above are examined critically in relation to the present state of π-electron resonance theory, taking up the several types of evidence considered by Dewar. The examination discloses no adequate reasons for believing, and some for disbelieving, that π-electron resonance is of negligible importance in causing the observed phenomena in ordinary conjugation and hyperconjugation (isovalent conjugation and hyperconjugation are not considered here). Rather, it appears that π-electron resonance and other causes may be of comparable importance. Dewar's challenge has in any event made clear the importance of a careful re-examination of the theoretical basis of conjugation, hyperconjugation, and related phenomena.

Bond Lengths

Basically, the factors governing the exact values of bond lengths are not well understood theoretically. There is no good theoretical basis for the idea of an accurately constant covalent bond radius for an atom even when it is using a particular definite bond orbital (or orbitals). A survey of actual bond lengths shows that the concept of definite bond radii is on the whole justified as an approximateion, but that even when allowances are made for ionic character or other reasonably assignable structural causes, many anomalies remain. Consider for example the following values of the covalent radius r_c obtained for the H atom in various bonds AH when the covalent radius of the A atom is taken as half the length of the bond in A—A:

From	r_c (Å)
H_2	0·37
CH in CH_4	0·32*
LiH	0·26
HI	0·27
HCl	0·28
HF	0·20

* Using the C—C bond length for C_2H_6

[7] R. S. Mulliken, Report at Conference on Hyperconjugation, Bloomington, Indiana, June, 1958. *Tetrahedron* **5**, 253 (1959)

VOL. 6 1959

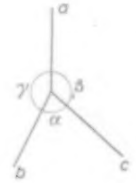
In view of the rather sketchy basis for the assumption that a given bond orbital should have a fixed "bond radius", Dewar's proposal that the bond radii of carbon for "trigonal" and "digonal" bond orbitals are considerably smaller in C—C than in C—H bonds cannot be considered very unreasonable.

Hybridization and bond lengths

A rather plausible alternative is the possibility that the actual state of hybridization is not the same for "trigonal" or "digonal" carbon in C—H as in C—C bonds. The observed bond lengths (those for C—C bonds should first be corrected for π-electron resonance, see below) might be consistently understood if in C—H and C—C bonds both deviate from true trigonal or digonal hybridization in the direction of tetrahedral hybridization, but with a *greater* deviation (less *s* and more *p* character) in the C—H bonds. The current widely accepted belief that carbon σ orbitals are definitely either tetrahedral in $\rangle$C$\langle$, trigonal in $\rangle$C=, or digonal in —C≡ or =C= situations, has little to recommend it beyond simplicity.

The belief in trigonal orbitals in $\rangle$C= situations is based on the fact that observed bond angles around the C atom are near 120°. For 120° angles, *assuming* (1) that the carbon σ orbitals extend out in the directions of the bonds and (2) that the overall valence structure is sp^3, and noting that the π bond is formed by a pure *p* orbital, one concludes that the carbon orbitals of the three σ bonds are equivalent; and if so, they are necessarily trigonal hybrids. However, actual bond angles often deviate appreciably from 120°.

For the case of a planar molecule with bond angles α, β, γ, Coulson[4] gives the



following equations for the "hybridization ratio" λ in a hybrid orbital of the form $s + \lambda p\sigma$:

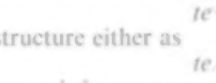
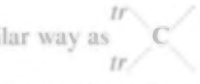
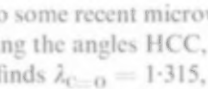
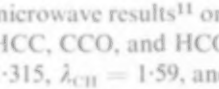
$$\lambda_a = [-\cos\alpha/\cos\beta\cos\gamma]^{\frac{1}{2}}, \qquad \lambda_b = [-\cos\beta/\cos\alpha\cos\gamma]^{\frac{1}{2}},$$
$$\lambda_c = [-\cos\gamma/\cos\alpha\cos\beta] \qquad (1)$$

where *a*, *b*, *c* refer to the carbon bond orbitals pointing in the directions indicated by the figure. According to recent careful determinations for ethylene, α is 117·37° ± 1°, R C=C = C is 1·337 ± 0·003 Å, and R_{CH} is 1·086 ± 0·003 Å (Allen and Plyler[8]), or $\alpha = 116° \pm 1°$, $R_{CC} = 1{\cdot}334 \pm 0{\cdot}003$ Å, $R_{CH} = 1{\cdot}085 \pm 0{\cdot}005$ Å (Bartell and Bonham[9]). Taking $\alpha = 117°$, $\beta = \gamma = 121{\cdot}5°$, one obtains $\lambda_{CC} = 1{\cdot}29$ and $\lambda_{CH} = 1{\cdot}48$, as compared with 1·00, $\sqrt{2}$, and $\sqrt{3}$ for digonal, trigonal, and tetrahedral

[8] H. C. Allen, Jr. and E. K. Plyler, *J. Amer. Chem. Soc.* **80**, 2673 (1958). Infrared spectrum.
[9] L. S. Bartell and R. A. Bonham, *J. Chem. Phys.* **27**, 1414 (1957). Electron diffraction.

hybrids. This indicates that the C—H bond is intermediate between trigonal and tetrahedral, although nearer the former, and the C=C σ bond between trigonal and digonal, although nearer the former.

In ethylene *derivatives*, the literature indicates (although one should probably await verification with the best modern techniques before reaching final conclusions) that smaller values of α than 120°, and larger values of β and γ, are the rule rather than the exception. For example, Pauling and Brockway[10] by electron diffraction obtained $\alpha = 110{\cdot}5 \pm 2°$ (hence $\beta = \gamma = 124°$) in tetramethylethylene. Equation (1) then gives $\lambda = 1{\cdot}08$ (close to digonal) for the C=C bond, and $\lambda = 1{\cdot}65$ (close to tetrahedral) for the C—C bonds.

These deviations from trigonal bond angles would correspond to a tendency of the carbon atom to have always four equivalent *te* (tetrahedral) bond orbitals. If this tendency were completely realized, the left-hand carbon in would use two equivalent *te* orbitals in the molecule plane for the bonds to *b* and *c* (angle *bCc* 109°28′) and two others perpendicular to the plane to form the double bond. This is the old original bent-bond model which uses two equivalent *te* orbitals from each atom to form the double bond. A single electron in a *te* orbital may conveniently be called an $s^{\frac{1}{4}}p^{\frac{3}{4}}$ electron, and two such electrons embody a population distribution $s^{\frac{1}{2}}p^{\frac{3}{2}}$. Quantum-mechanically an $s^{\frac{1}{2}}p^{\frac{3}{2}}$ bent-bond C= structure is completely equivalent to a σ, π structure, provided (since the π electron contributes 1·00 to the *p* population) the σ orbital is digonal ($s^{\frac{1}{2}}p^{\frac{1}{2}}$), and thus non-equivalent to the $s^{\frac{1}{4}}p^{\frac{3}{4}}$ σ orbitals of the *b* and *c* bonds. The actual C= structures in ethylene and its derivatives apparently are compromises between the structure just discussed and the 120°-angle structure with three equivalent σ orbitals. Using the symbols *tr* and *di* to represent $s^{\frac{1}{3}}p^{\frac{2}{3}}$ and $s^{\frac{1}{2}}p^{\frac{1}{2}}$ orbitals of σ type, one may describe the first structure either as  *or* as  , and the second in a similar way as  *or* as  .

The application of equation (1) to some recent microwave results[11] on the structure of CH_3CHO is of interest. Identifying the angles HCC, CCO, and HCO of the HCO group with α, β, γ respectively, one finds $\lambda_{C=O} = 1{\cdot}315$, $\lambda_{CH} = 1{\cdot}59$, and $\lambda_{CC} = 1{\cdot}36$, as compared with $\lambda_{C=C} = 1{\cdot}29$ and $\lambda_{CH} = 1{\cdot}48$ for C_2H_4 (see above) and $\lambda = 1{\cdot}414$ for pure *tr* and 1·732 for pure *te*. The difference between the C—H and C—C bonds here is striking: the σ bond orbital in CH seems to be nearer to *te* than to *tr*, while that in C—C has even a little more *s* character than *tr*.

In linear molecules of structures *a*—C≡*b*, bond angles can give no guidance (although perhaps force constants could). Equation (1) is here replaced by

$$\lambda_a \lambda_b = 1. \tag{2}$$

If the σ bonds C—*a* and C—*b* are equivalent, then both are digonal ($\alpha = 1$). The

[10] L. Pauling and L. O. Brockway, *J. Amer. Chem. Soc.* **59**, 1223 (1937).
[11] R. W. Kilb, C. C. Lin, and E. B. Wilson, Jr., *J. Chem. Phys.* **26**, 1695 (1957).

structure is $di\text{—}\overset{\overset{-\pi}{|}}{\underset{\underset{-\pi}{|}}{C}}\text{—}di$, equivalent to $di\text{—}C\begin{cases}s^{\frac{1}{3}}p^{\frac{2}{3}}\\ s^{\frac{1}{3}}p^{\frac{2}{3}}\\ s^{\frac{1}{3}}p^{\frac{2}{3}}\end{cases}$. On the other hand, the bent-

bond model using tetrahedral orbitals $te\text{—}C\begin{cases}te\\ te\\ te\end{cases}$ is equivalent to $te\text{—}\overset{\overset{-\pi}{|}}{\underset{\underset{-\pi}{|}}{C}}\text{—}s^{\frac{1}{2}}p^{\frac{1}{2}}$, the

σ orbital of the C≡ bond having even more s character than di. Although variations in bond angles are not available as a guide here, it seems likely that the hybrids in actual molecules lie between those of the two cases discussed.

We may ask *why* carbon atom σ orbitals forming C—H and C—C single bonds in unsaturated systems should depart to different extents from the trigonal or digonal ideal. Such differences could perhaps occur because of the different electronegativities of H 1*s* and C 2*s* and 2*p* orbitals, or because of failure of the two assumptions made at the outset of the foregoing discussion. Assumption (1) is essentially that single bonds are never bent bonds, with the obvious exception of cyclic systems, of which *cyclo*propane is a notable example. But if strongly bent bonds are tolerated in *cyclo*propane and in double and triple bonds when the description in terms of equivalent bond orbitals is used, it is not clear why they cannot occur also in ordinary single bonds. For example, in ethylene the principle of maximum overlap of bond orbitals would, it is true, cause the H atoms to be located on the symmetry axes of the appropriate hybrid carbon σ orbitals, but nonbonded repulsions between H atoms might displace them from these locations, and there seems to be no reason why the hybridizations should change to accommodate fully to these changed locations. With regard to assumption (2), we know that actual carbon valence atom states are partially s^2p^2 (and p^4), not all sp^3, and there is also a little s^2p^3, p^5, and sp^4 due to polarity of CH bonds.[12] It seems entirely possible that failure of the two assumptions just discussed may be responsible for quite appreciable effects, which also may differ for C—H and C—C bonds and lead to differences in carbon orbital hybrid character and bond lengths in the two cases.

While the preceding discussion has led to little in the way of positive conclusions, it underlines the dangers of oversimplified explanations which do not consider all factors. A really full and clear understanding of bond lengths will probably not be available until accurate wave functions have been obtained by extensive quantum-mechanical calculations.

However, it does seem possible to reach some fairly definite conclusions about the effect of π-electron resonance on bond lengths. Fortunately, the particular hybrid character of accompanying σ bonds does not enter into the theory of π-electron resonance, except only in so far as it affects the "natural" lengths of σ bonds: shorter σ bonds result in somewhat stronger π-electron resonance.

Effects of π-electron resonance on bond lengths

Dewar's account of C—C bond lengths, as summarized in the Introduction, has the advantages (and the dangers) of simplicity, but he apparently also feels that the empirically observed *constancies* of C—C, and of C=C and C≡C, bond lengths within specific types of conjugated and hyperconjugated compounds contradict what one would expect from π-electron resonance theory. A careful examination of the

[12] H. H. Voge, *J. Chem. Phys.* **4**, 581 (1936); **16**, 984 (1948); M. Kotani and K. Siga, *Proc. Phys. Math. Soc. Japan* **19**, 471 (1937).

theory in its present state fails to support this view. If the predicted effects of π-electron resonance were as large as in the early calculations of the simple Hückel theory, the observed constancies *would* be very difficult to understand, but on the basis of calculations by the LCAO-SCF, Pariser–Parr, Pople and similar methods, they are entirely consistent with π-electron theory, as will be shown below. The observed constancies remain surprising only in view of the unreliability *in general* of predictions from fixed covalent radii; one would not have been surprised at considerable departures from constancy as a result of *other* causes than π-electron resonance.

Let us first consider *conjugated* C—C bonds. As a result of numerous computations on 1:3-butadiene, one can arrive at rather definite conclusions. In a single-determinant wave function, the two occupied π MOs of butadiene have the forms:

$$\phi_1 = a_1\chi_a + b_1\chi_b + b_1\chi_c + a_1\chi_d; \quad \phi_2 = a_2\chi_a + b_2\chi_b - b_2\chi_c - a_2\chi_d, \qquad (3)$$

where a, b, c, d refer to the four carbon atoms. Table 1 contains the results obtained for these coefficients by various authors, and also the corresponding Coulson LCAO bond orders. The first three computations listed were by the semiempirical Hückel method, neglecting overlap; they differ through varying assumptions about how the

TABLE 1. LCAO–MO COEFFICIENTS AND BOND ORDERS BASED ON COMPUTATIONS BY VARIOUS AUTHORS (COEFFICIENTS NORMALIZED CORRESPONDING TO ZERO OVERLAP)

Author	Coefficients				Bond orders*		R Values assumed
	a_1	b_1	a_2	b_2	ab or cd	bc	
Hückel	0·372	0·601	0·601	0·372	0·894	0·447	equal
Lennard-Jones	0·401	0·582	0·582	0·401	0·934	0·356	1·44, 1·35
Mulliken, Rieke and Brown[a]	0·411	0·576	0·576	0·411	0·945	0·325	1·46, 1·35
Pople[b]	0·4246	0·5655	0·5655	0·4246	0·960	0·279	
Parr and Mulliken[c]	0·426	0·564	0·543	0·452	0·972	0·227	1·46, 1·35
Kon[d]					0·974	0·227	
Moser[e]	0·426	0·564	0·536	0·461	0·975	0·211	1·46, 1·35
Berry LCAO–SCF[f]	0·410	0·576	0·541	0·455	0·965	0·251	1·46, 1·35
Berry AIM[f]	0·466	0·534	0·561	0·429	0·978	0·202	1·46, 1·35

* $2(a_1b_1 + a_2b_2)$ for bond ab or cd; $2(b_1^2 - b_2^2)$ for bond bc.
[a] Ref. 4. [b] J. A. Pople, *Trans. Faraday Soc.* **49**, 1375 (1953). [c] Ref. 13. [d] H. Kon, *Bull. Chem. Soc. Japan* **28**, 275 (1955). [e] C. M. Moser, *J. Chem. Soc.* 3455 (1954). [f] Ref. 14.

resonance integral β varies with carbon–carbon distance R. Hückel assumed it constant, Lennard-Jones, and Mulliken *et al.* used empirical evidence to determine a functional relation $\beta(R)$. Parr and Mulliken[13] made an LCAO–SCF Slater–AO π-electron computation assuming a Goeppert–Mayer–Sklar type of σ-electron-core field. In Table 1, their coefficients (which take account of overlap) have been renormalized (as have those of Berry) in such a way that $2(a_i^2 + b_i^2) = 1$ ($i = 1$ or 2), since this is necessary in order to obtain Coulson bond orders (Table 1, footnote*). Later computations (Pople, Kon, Moser, Berry AIM, (atoms-in-molecules)) by the Pariser–Parr and similar methods (all formally neglect overlap), designed to correct by semiempirical procedures for the faults of the LCAO–SCF method, give

[13] R. G. Parr and R. S. Mulliken, *J. Chem. Phys.* **18**, 1338 (1950).

coefficients, and in particular bond orders, which agree well with those of Parr and Mulliken. Since all these methods take account specifically of electronic interactions, it would seem that one can place considerable reliance on the resulting bond orders as substantially correct; Moser's result of 0·975 for the C=C bonds and 0·21 for the C—C bond may be taken as representative.

Further refinements in the theory might of course alter one's opinion somewhat. Dewar has suggested that more accurate allowance for interelectronic repulsions and for correlation energy (as shown e.g. by configuration interaction) than in the Parr and Mulliken calculation might reduce the C—C bond order to nearly zero. However, the results of the various subsequent calculations listed in Table 1, indicate that these effects are of minor importance. In fact, a recent as yet unpublished analysis by Berry of wave functions he had previously obtained[14] shows that configuration interaction actually increases the amount of double bond character in the central bond in butadiene, as compared with a single-determinant wave function.

VOL. 6 1959

Given the Coulson bond orders, one can use a standard bond-order bond-length curve to estimate the effects of π-electron resonance on bond lengths. (More properly, one should use a somewhat shifted curve (cf. e.g. Coulson[4]) for each state of hybridization; but since these curves are probably nearly parallel, this makes no real difference for present purposes.) For the C—C bond lengths, one obtains a predicted shortening of 0·04 Å using the C—C end of the curve (based on C_2H_6), or perhaps 0·035 Å in view of the evidence that the "natural length" of the *tr-tr* C—C bond is somewhat shorter than for a *te-te* C—C bond. (Here and from this point on, the symbols *te*, *tr*, and *di* should be taken as merely conventional, subject to all the qualifications and uncertainties outlined in the paragraphs above on "Hybridization and Bond Lengths.") With correct values of the actual C—C and C=C bond lengths in butadiene (1·483 $\pm$ <0·01 and 1·337 $\pm$ 0·0005 Å)[3] instead of those assumed in the calculations summarized in Table 1, the calculated C—C π bond order would be a little smaller, and the predicted π delocalization shortening reduced perhaps to 0·03 Å. The "natural length" of a *tr-tr* C—C bond then comes out to be 1·51 $\pm$ 0·01 Å.

In the absence of any Pariser–Parr or LCAO–SCF calculations for diacetylene, one can only estimate roughly, by assuming a parallelism to Table 1, how the earlier results (Hückel, Mulliken–Rieke–Brown) would be modified in such a calculation. The so estimated π bond orders are, 0·43 for the C—C bonds and 1·947 for the C≡C bonds. Using the bond-order bond-length curve, the predicted π-delocalization shortening for the C—C bond is then about 0·07 Å. With an *observed* length of 1·38 Å, one obtains a "natural length" for a *di-di* C—C bond of about 1·45 Å, as compared with about 1·51 Å for a *tr-tr* and 1·54 Å for a *te-te* C—C bond.*

In a similar way for *hyperconjugation*, the following rough estimates can be made. For the C—C bond in propylene, π bond order 0·066, predicted shortening 0·01 Å; for the C—C bond in methylacetylene, π bond order 0·154, shortening 0·025 Å. Using observed bond lengths, one then obtains 1·51 and 1·485 Å for the "natural lengths" of the respectively *te-tr* and *te-di* C—C bonds in these molecules.

The foregoing estimates of π-electron resonance shortening in ordinary conjugation and hyperconjugation suggest that observed shortenings should be expressible

* Incidentally, the shortenings thus obtained from *te-te* to *tr-tr* and *di-di* agree very closely with values computed theoretically by Coulson[4] by considering the charge centroids of *te*, *tr*, and *di* hybrid σ AO's.

[14] R. S. Berry, *J. Chem. Phys.* **26** 1660 (1957).

as a sum of resonance and hybridization shortenings of comparable magnitude. Table 2 shows that formulas based on this idea give good agreement with observed shortenings, especially when allowance is made for the fact that molecules having the same bond pattern do *not* always show the same shortening within experimental error. The coefficients in the formulas used in Table 2 attribute roughly 40 per cent of observed shortenings to π-electron resonance, 60 per cent to hybridization. The observed shortenings in Table 2 A are respectively somewhat higher or lower than the calculated for the hyperconjugated type *te-tr* and the conjugated type *tr-tr*. However, the observed values in each case are based on a single molecule. In the hyperconjugated case, the bond angles for CH_3HCO indicate *more* than *tr s* character in the "*tr*" orbital (see discussion in an earlier paragraph), which perhaps explains the large observed ΔR. (Already earlier,[15] Mulliken suggested 0·03 Å hybridization shortening in butadiene.)

TABLE 2. SHORTENINGS (Å.U.) OF CONJUGATED BONDS

A. C—C *Bonds*

Bond patterns	Calculated $-\Delta R$(Å.U.)[a]					Observed[b,c]	
	an_{tr}	bn_{di}	cN_{cj}	dN_{HCj}	Total	$-\Delta R$	Molecules
H_2C—CH═ (*te-tr*)	0·02			0·015	0·035	0·043 ± 0·002	H_3CCHO only
H_2C—C≡ (*te-di*)		0·05		0·03	0·08	0·084	CH_3CN, $CH_3C{\equiv}CH$
═HC—CH═ (*tr-tr*)	0·04		0·035		0·075	0·061 ± <0·01	Butadiene
═HC—C≡ (*tr-di*)	0·02	0·05	0·035		0·105	0·098 ± 0·001	O═CH—C≡CH
						0·119 ± 0·001	H_2C═CH—C≡N
═C—C≡ (*di-di*)		0·10	0·07		0·17	0·166 ± 0·001	N≡C—C≡CH, etc.

B. C═C *Bonds*

H_2C═C═ (*tr-di*)		0·018		0·01	0·03	0·027 ± 0·001	Allene
═C═C═ (*di-di*)		0·035	0·025		0·06	0·058	C_3O_2

[a] For case A(C—C bonds), from $-\Delta R = 0{\cdot}02n_{tr} + 0{\cdot}05n_{di} + 0{\cdot}035N_{cj} + 0{\cdot}015N_{HCj}$, where n_{tr} and n_{di} are the numbers of "trigonal" or "digonal" atoms, and N_{cj} and N_{HCj} are the numbers of dimensions of conjugation or first-order hyperconjugation. For case B(C═C bonds), from $-\Delta R = 0{\cdot}018n_{di} + 0{\cdot}025N_{cj} + 0{\cdot}01\,N_{HCj}$.

[b] For C—C bonds, relative to 1·544 Å assumed for R_{CC} in C_2H_6. For C═C bonds, relative to 1·337 Å for R_{CC} in C_2H_4 (cf. ref. 8).

[c] From selected R_0 values believed by B. Stoicheff to be good to ±0·005 Å.U. or better. Butadiene and C_3O_2 from unpublished R_a values by O. Bastiansen.

Part B of Table 2 deals with the fact that conjugative (for internal) and hyperconjugative (for $=CH_2$ terminal) shortenings of cumulated C═C bonds are expected and observed. Both resonance and hybridization shortenings might reasonably be expected to be smaller than for C—C bonds, because the σ bond in a C═C bond is already under compression by the π bond. A plausible formula in line with this expectation reproduces observed shortenings.

It appears likely that observed conjugation and hyperconjugation shortenings, even after all have been brought to the highest possible accuracy, will not in themselves provide definitive evidence as to the relative importance of resonance and

[15] R. S. Mulliken, *J. Chem. Phys.* **23**, 2343 (1955); **23**, 1841 (1955).

hybridization. We will probably have to be guided by theory. But in any event there seems to be no inconsistency between observed shortenings and present predictions of theory. However, LCAO–SCF calculations on π bond orders will be desirable in the several cases, other than =C—C= in butadiene, where they have not yet been made.

Although the symbols *te*, *tr*, and *di* in Table 2 refer ostensibly to tetrahedral, trigonal, and digonal hybrids, it is well to keep constantly in mind that the actual hybrids involved may be rather different.

Turning now from the inner or acceptor bonds to the outer or donor bonds in conjugation and hyperconjugation, the usual π-electron theory predicts that if the former are shortened by resonance, the latter should be somewhat lengthened. For the case of butadiene, one may refer to the *ab* bond orders in Table 2, and then use the bond-order bond-length curve to find the predicted lengthening of the C=C bonds. With the Mulliken–Parr or Moser bond order, the predicted lengthening is only 0·004 Å, as contrasted with 0·02 Å if one had used the bond order from the Hückel calculation. Similarly, the C=C bond order 1·947 estimated above for diacetylene corresponds to a predicted lengthening of only 0·006 Å from the C=C length in acetylene. Thus the presently predicted bond order changes for *multiple* bonds in conjugation (all the more so in hyperconjugation) are comparable with experimental error, in contrast to the Hückel predictions which were large enough to furnish Burawoy[2] with what seemed a serious objection to π-electron resonance theory.

But even the small predicted increases just indicated for the lengths of *multiple* bonds should in fact be reduced (or possibly even changed to small decreases) in a more accurate π-electron theory treatment. Very briefly, the argument runs as follows.* In a conjugated molecule such as butadiene, if there were no π-electron resonance, the juxtaposition of two double bonds would introduce according to VB theory a nonbonded repulsion between the adjacent π electrons at opposite ends of the single bond. As compared with an isolated double bond as in ethylene, this would increase the π-electron density within each double bond somewhat, and so strengthen and no doubt shorten it correspondingly. Although no VB calculations are available, LCAO–MO calculations show that in the assumed absence of π-electron resonance, the "overlap populations" in the C=C bonds in butadiene are distinctly greater than those in ethylene.[15] This result appears to confirm the statement just made in terms of VB theory. However, π-electron resonance tends to reverse this shortening effect on the C=C bonds by transferring some π-electron density into the C—C bond, and the net result of both effects may well be either a slight shortening or a slight lengthening, or almost no change, of the C=C bond length as compared with ethylene. Similar considerations apply for the lengths of conjugated triple bonds as compared with the C≡C bond in acetylene.

In all of the preceding discussion, nothing has been said about σ-electron delocalization effects. These of course must have had some effect on the "natural" lengths of all C—C bonds, but this point need not seriously concern us if we are interested primarily in π-electron delocalization (resonance) effects. Also, there is no obvious reason why σ-delocalization effects should be much different for different kinds of C—C bonds.

* A full explanation of the small but interesting effect in question would be rather lengthy, and will be reserved for a separate paper.

More relevant is the fact that second-order π_x and/or π_y hyperconjugative resonance should be universally present for C—C bonds whenever corresponding conjugative or first-order hyperconjugative resonance is absent. This must be kept in mind in connection with "natural lengths" of C—C bonds discussed above following Table 1. To be consistent, the true natural length of *te-te* C—C bonds, as in C_2H_6, must be considered slightly greater than the actual C—C bond length in C_2H_6. However, the π bond orders due to second-order hyperconjugative delocalization are small according to the more recent computations.

CONCLUSIONS

The foregoing review of π-electron theory predictions indicates that Dewar is partly right in supposing that, to a greater extent than previously supposed, the lengths of conjugated and hyperconjugated C—C bonds are determined by the states of hybridization of the carbon bond orbitals rather than by π-electron resonance. However, there seems to be no justification for Dewar's assumption that the π-delocalization shortenings in conjugation and hyperconjugation are negligible. The observed approximate constancy of C—C bond lengths for carbon atoms with orbitals in particular states of hybridization is not inconsistent with π-electron delocalization predictions, except apparently in the case of *cyclo*octatetraene. (However, twisting of two adjacent double bonds so that their planes become perpendicular (as is approximately true in *cyclo*octatetraene), although it destroys conjugation, creates first-order hyperconjugation at *both* ends of the C—C bond: each —C= after twisting functions, like a $-CH_3$ group in propylene, to give hyperconjugation across the C—C bond with the C=C π electrons of the other =CH— group. Thus some resonance shortening is still expected.*) But in any event the observed C—C bond lengths in *cyclo*octatetraene (1·46 Å as compared with 1·48 Å for butadiene) are anomalous even in terms of Dewar's proposals.

The observed constancy of C—C bond lengths in such hyperconjugated systems as Me_3C—C≡CH, Cl_3C—C≡CH, H_3C—C≡CH, F_3C—C≡N, H_3C—C≡N is not inconsistent with reasonable expectations from π-electron theory which, contrary to the ideas of Baker and Nathan, would not suggest radically diverse degrees of hyperconjugative delocalization for CH_3, CMe_3, CCl_3, etc. Finally, the observed constancy of C=C and C≡C bond lengths in conjugated systems and their close agreement with the lengths in C_2H_4 and C_2H_2 are precisely what would be expected from a correct application of π-electron theory.

Bond Energies

Significance of bond energy formulas

Central to any consideration of "empirical resonance energies" is a standard formula for heats of formation, or atomization energies, or heats of combustion.[17] For atomization energies, taking energy given out as positive, such a formula for any hydrocarbon may be written as follows:

$$B = HN_{CH} + SN_{C-C} + DN_{C=C} + TN_{C\equiv C} + \Delta \qquad (4)$$

* On the other hand, data cited[16] indicate a progressive lengthening of the C—C bond in substituted diphenyls with progressive increase in twist angle caused by steric repulsion of *o*-substituents. However, perhaps the lengthening here is a by-product of the steric repulsion.

[16] D. Cook, *J. Chem. Phys.* **28**, 1001 (1958).

[17] R. S. Mulliken and R. G. Parr, *J. Chem. Phys.* **19**, 1271 (1951).

The "bond energies" H and S are first chosen so as to fit with $\Delta \approx 0$ the experimental B for diamond and for two or three light unbranched paraffins, say propane, *n*-butane, and *n*-pentane.* D and T are then determined as follows:

$$D = B(C_2H_4) - 4H; \quad T = B(C_2H_2) - 2H \tag{5}$$

H, S, D, and T chosen in the manner just specified are now assumed to be constant for all hydrocarbons. After deducting any systematic deviations which are believed assignable to causes other than π-electron resonance (e.g. branching in paraffins, or steric effects; obviously this is a matter of judgment), the remainder of Δ is commonly interpreted as due to stabilization by π-electron resonance ("vertical delocalization energy" minus the "compression energy" required to change σ bond lengths from their "natural" values to observed values).

Equations (4) and (5) seem to imply that all C—H bonds have the same strength H and all C—C bonds the same strength S. Actually, as many people who have worked with equation (4) have doubtless realized, no such implication is necessarily involved.

To see this, let us first generalize equation (4) by assuming different values of H and S depending on the states of hybridization believed to exist in the carbon σ orbitals involved. If H_1, H_2, and H_3 refer to "*te*", "*tr*", and "*di*" C—H bonds, and S_{11}, S_{12}, S_{13}, S_{22}, S_{23}, and S_{33} to *te-te*, *te-tr*, *te-di*, *tr-tr*, *tr-di*, and *di-di* C—C bonds, we have (letting i and j take on values 1, 2 and 3):

$$B = \sum_i H_i N_i(\text{CH}) + \sum_{i,j} S_{ij} N_{ij}(\text{C—C}) + D_{22}\text{N(C=C)} + T_{33}\text{N(C}\equiv\text{C)} + \Lambda \tag{6}$$

The various coefficients H_1, H_2, H_3, S_{11}, and so on, are now assumed to be constants valid for all hydrocarbons. (For cumulenes, D_{22}N(C=C) should be replaced by $\sum_{i,j} D_{ij} N_{ij}$(C=C), with i, j having values 2, 3 only). Λ of equation (6) plays the same role as Δ of equation (4), but need not be equal to Δ; since equation (6) should have greater validity than equation (4), Λ should be a better measure of π-electron resonance energy than Δ, if they differ. H_1 and S_{11} of equation (6) are identical with H and S of equation (4), and D_{22} and T_{33} are related to D, T, and H of equations (4) and (5) by

$$\begin{aligned} D_{22} &= B(C_2H_4) - 4H_2 = D - 4(H_2 - H); \\ T_{33} &= B(C_2H_2) - 2H_3 = T - 2(H_3 - H). \end{aligned} \tag{7}$$

Without necessarily assuming that the H's and S's are independent of hybridization, equations (6), (7), reduce to equation (4) under certain not unplausible assumptions. This can be more readily understood by considering two specific examples, 1:3-butadiene and propylene. For these, using equations (6) and (7), we have:

$$\left.\begin{aligned} B(C_4H_6) &= 6H_2 + S_{22} + 2D_{22} + \Delta \\ &= 6H + S + 2D + \{[(S_{22} - S) - 2(H_2 - H)] + \Lambda\} \\ B(C_3H_6) &= 3H + 3H_2 + S_{12} + D_{22} + \Delta \\ &= 6H + S + D + \{[S_{12} - S) - (H_2 - H)] + \Lambda\} \end{aligned}\right\} \tag{8}$$

* Actually, absolute B values are still not accurately known, but this uncertainty involves only an additive constant and does not matter here. However, corrections to eliminate thermal and zero-point energy should be, but usually are not, made.

Note that the quantities in curly brackets in equations (8) correspond to Δ of equation (4).

If it it assumed that the quantities in *square* brackets in equations (8), and similar quantities in other cases, are equal to zero, then equation (4) always holds for hydrocarbons (other than cumulenes), with Δ equal to Λ of equation (6). This assumption would be correct if (a), hybrid orbitals of each kind (*te*, *tr*, or *di*) are the same in C—H and C—C bonds, and (b), C—H and C—C bond strengths are equally altered for any given change in hybridization of any one carbon bond orbital. (For a C—C bond, two carbon bond orbitals are of course involved). Those who have used equation (4) to determine "resonance energies" Δ have had, knowingly or not, the justification that this apparently oversimplified equation is equivalent to the much more acceptable equation (6) coupled with the at first sight not unplausible assumption just discussed (but see next section).

Dewar, on the other hand, arguing from the fact that carbon covalent radii seem to be shortened much more in conjugated C—C bonds than in C—H bonds involving supposedly the same hybrid carbon bond orbitals, assumes that the *bond energy* differences for C—C bonds also are much greater, and in fact to such an extent that he assumes $H_3 - H_1 = H_2 - H_1 = 0$. This, combined with the assumption that the π-electron resonance energy is negligible, i.e. $\Lambda = 0$ in equations (6) and (8), permits him (cf. equations 8) to identify the deviations Δ from equation (4) with C—C bond energy changes such as $S_{22} - S_{11}$ for butadiene or $S_{12} - S_{11}$ for propylene. He believes that these and certain other assumptions are justified by the self-consistency of the results obtained.

Until Dewar's paper is published, it is not possible to pass judgment on the strength of these arguments of self-consistency. A priori, however, Dewar's assumptions certainly appear to be at least as arbitrary as those involved in the supposition that Δ of equation (4) (after correction for steric effects, etc.) represents exclusively π-electron resonance energy. In proposing that the quantities Δ shall be called "stabilization energies", rather than resonance energies, Dewar is certainly right in principle. But there seem to be no sufficient reasons to deny that π-electron delocalization may make an important contribution to observed Δ's in conjugated and hyperconjugated systems.

Expected polar contributions to bond energies

In fact, reasons can be given for believing that π-electron delocalization energies Λ may often be *larger* than observed Δ's, rather than smaller. Namely, as will be shown below, one might reasonably expect considerable *negative* contributions to Δ to be present corresponding to the *polar excess bond energies* (Pauling's Δ quantities as used in the empirical basis of his electronegativity scale) of C^{di}—H and C^{tr}—H as compared with C^{te}—H bonds. For example, in equations (8), the greater polarity of *tr*—H as compared with *te*—H should result in a net polar contribution increasing $H_2 - H_1$ (partially compensated in propylene by a polar contribution from $S_{12} - S$). This increase tends to make Δ smaller than Λ. Similar but *larger* effects are expected for conjugation or hyperconjugation involving triple bonds.

Even on quite general grounds, it seems unsafe to argue that because C—H bond *lengths* show relatively small changes with state of hybridization of the carbon orbital,

one must expect C—H bond *energies* to be equally insensitive to hybridization. Such a parallelism would seem possible, but not particularly probable.

One positive reason *against* it lies in the existence of familar examples where bond energy increases markedly with increasing polarity, without notable corresponding effects on bond lengths. Thus, $R_{HI} = 1/2(R_{HH} + R_{II}) - 0{\cdot}10$ Å and $B_{HI} = \frac{1}{2}(B_{HH} + B_{II}) + 2$ kcal, while $R_{HCl} = \frac{1}{2}(R_{HH} + R_{ClCl}) - 0{\cdot}09$ Å and $B_{HCl} = \frac{1}{2}(B_{HH} + B_{ClCl}) + 22$ kcal. Because of its greater polarity perhaps even more than because of its greater *s* character, one might expect H_2 to exceed H_1. On the other hand, if the *s* character of the carbon bond orbital in C^{tr}—H is less than in C^{tr}—C^{tr}, as seems likely on the basis of the discussion earlier in this paper, the magnitude of $H_2 - H_1$ would be less for both reasons; also it may well vary from case to case. Still, there seems to be no reason why it should be negligible.

VOL. 6 1959

Equations (8) are special cases of the following general equation which can be obtained by systematically substituting equations (7) into equation (6):

$$\begin{aligned} B = {} & H\mathrm{N(CH)} + S\mathrm{N(C{-}C)} + D\mathrm{N(C{=}C)} + T\mathrm{N(C{\equiv}C)} \\ & + \sum_{i \neq 1} (H_i - H)\mathrm{N}_i\mathrm{(C{-}H)} + \sum_{i \neq 1, j \neq 1} (S_{ij} - S)\mathrm{N}_{ij}\mathrm{(C{-}C)} \\ & - 4(H_2 - H)\mathrm{N}_{22}\mathrm{(C{=}C)} - 2(H_3 - H)\mathrm{N(C{\equiv}C)} + \Lambda \end{aligned} \tag{9}$$

(For cumulenes, add $(D_{23} - D)\mathrm{N}_{23}\mathrm{(C{=}C)} + (D_{33} - D)\mathrm{N}_{33}\mathrm{(C{=}C)}$. Equation (9) consists of the same major terms as equation (4), plus correction terms.

It will be recalled that Pauling found that the bond energies of polar bonds between atoms Y and Z can be represented rather well by

$$B\mathrm{(Y{-}Z)} = \tfrac{1}{2}[B\mathrm{(Y{-}Y)} + B\mathrm{(Z{-}Z)}] + \Gamma_{YZ};\ \Gamma_{YZ} = \gamma(X_Y - X_Z)^2, \tag{10}$$

γ being a universal constant and X_Y and X_Z being identified as the electronegativities of atoms Y and Z. (The symbol Γ is used here, rather than Pauling's Δ, to avoid confusion with Δ of equation 4.) As various people have pointed out, different carbon hybrid σ orbitals should differ in electronegativity,[18] hence H_i (including $\mathrm{H{\equiv}H_1}$) and S_{ij} in equation (9) should be expressible as

$$H_i = \tfrac{1}{2}[S_{ii}' + B(\mathrm{H_2})] + \Gamma_{i\mathrm{H}}';\quad S_{ij} = \tfrac{1}{2}(S_{ii}'' + S_{jj}'') + \Gamma_{ij}''. \tag{11}$$

Here *i*, *j* refer to *te*, *tr*, or *di* hybrid carbon orbitals (1 for *te*, 2 for *tr*, 3 for *di*). Indices ′ and ″ have been added to provide for the fact that the actual hybrids probably differ considerably from pure *te*, *tr*, and *di*, *and in different ways* for C—H and C—C bonds. The distinction can of course easily be dropped later. From equations (11), recalling that H means H_1, the following equations are readily obtained:

$$\left.\begin{aligned} H_i - H &= \tfrac{1}{2}(S_{ii}' - S) + (\Gamma_{i\mathrm{H}}' - \Gamma_{1\mathrm{H}}) \\ S_{ij} - S &= \tfrac{1}{2}(S_{ii}'' - S) + \tfrac{1}{2}(S_{jj}'' - S) + \Gamma_{ij}'' \\ D_{ij} - D &= \tfrac{1}{2}(D_{ii} + D_{jj}) - D + \Gamma_{ij}\ \text{(for cumulenes)} \end{aligned}\right\} \tag{12}$$

Substituting equations (12) into equation (9), one obtains *for the correction terms*

[18] R. S. Mulliken, *J. Chem. Phys.* **2**, 782 (1934); *J. Phys. Chem.* **41**, 318 (1937).

(Equation (9) minus equation (4)):

$$\left.\begin{aligned}
&[\tfrac{1}{2}(S_{22}' - S) + (\Gamma_{2II}' - \Gamma_{1II})]N_2(CH) + [\tfrac{1}{2}(S_{33}' - S) + (\Gamma_{3II}' - \Gamma_{1II})]N_3(CH)\\
&\quad + [\tfrac{1}{2}(S_{11}'' - S) + \tfrac{1}{2}(S_{22}'' - S) + \Gamma_{12}'']N_{12}(C{-}C) + (S_{22}'' - S)N_{22}(C{-}C)\\
&\quad + [\tfrac{1}{2}(S_{11}'' - S) + \tfrac{1}{2}[S_{33}'' - S) + \Gamma_{13}'']N_{13}(C-C) + [\tfrac{1}{2}(S_{22}'' - S)\\
&\quad + \tfrac{1}{2}(S_{33}'' - S) + \Gamma_{23}'']N_{23}(C{-}C) + (S_{33}'' - S)N_{33}(C{-}C)\\
&\quad - 4[\tfrac{1}{2}(S_{22}' - S) + (\Gamma_{2II}' - \Gamma_{1II})][N_{22}(C{=}C) + \tfrac{1}{2}N_{23}(C{=}C)]\\
&\quad + [\tfrac{1}{2}(D_{33} - D) + \Gamma_{23}]N_{23}(C{=}C) + (D_{33} - D)N_{33}(C{=}C)\\
&\quad - 2[\tfrac{1}{2}(S_{33}' - S) + (\Gamma_{3II'} - \Gamma_{1II})]N(C{\equiv}C) + \Lambda.
\end{aligned}\right\} \quad (13)$$

Now the numbers of bonds of various types in equation (13) are not entirely independent, but obey the relations

$$\left.\begin{aligned}
&N_2(CH) + N_{12}(C{-}C) + 2N_{22}(C{-}C) + N_{23}(C{-}C)\\
&\qquad = 4N_{22}(C{=}C) + 2N_{23}(C{=}C)\\
&N_3(CH) + N_{13}(C{-}C) + 2N_{23}(C{-}C) + N_{23}(C{-}C = 2N(C{\equiv}C).
\end{aligned}\right\} \quad (14)$$

If now we make the simplifying assumption that the hybrids "*te*", "*tr*", "*di*" are really pure *te*, *tr*, and *di* in both C—H and C—C bonds, so that $S_{ii}' - S_{ii}''$, and so on (including $S''_{11} - S) = 0$, expression (13) for the correction terms in equation (9) reduces with the help of equations (14) to

$$\begin{aligned}
&(\Gamma_{2II} - \Gamma_{1II})[N_2(CH) - 4N_{22}(C{=}C) - 2N_{23}(C{=}C)] + \Gamma'_{12}N_{12}(C{-}C)\\
&\quad + (\Gamma_{3II} - \Gamma_{1II})[N_3(CH) - 2N(C{\equiv}C)] + \Gamma_{13}N_{13}(C{-}C) + \Gamma_{23}[N_{23}(C{-}C)\\
&\quad + \tfrac{1}{2}N_{23}(C{=}C)] + (D_{33} - D)[\tfrac{1}{2}N_{23}(C{=}C) + N_{33}(C{=}C)] + \Lambda
\end{aligned} \quad (15)$$

If further, we ignore the polar terms (i.e. the Γ"s) in (15), nothing but Λ remains, except for cumulenes. This verifies for the general case the statement made immediately following equation (8), that equation (9) reduces to equation (4) with $\Delta = \Lambda$ if certain plausible assumptions are made.

Returning to (15), it is remarkable that (except for cumulenes) *only* polar terms and Λ remain as corrections to equation (4). However, if "*te*", "*tr*", and "*di*" hybrids are commonly quite different in C—H and C—C bonds, as seems likely from our earlier discussion, expression (13) is required, and it becomes almost impossible to draw any reliable conclusions from observed Δ values based on equation (4).

That the expected Γ"s and Γ' differences in (13) and (15) are often not small, especially where C—H bonds are concerned, can be seen from Table 3.

Possible usefulness of theory

All things considered, one is inclined to agree that Dewar and Schmeising are right in being skeptical about identifying Δ's from equation (4) with π-electron delocalization energies, but one is equally inclined to feel skeptical about accepting Dewar's new assumptions. Rather, it appears that a more thoroughgoing review of the whole situation is in order.

One now begins to wonder whether theoretical computations may not be a more reliable guide to actual delocalization energies than empirical Δ values. As we have seen in the previous Section, the purely theoretical LCAO–SCF calculations of Parr and Mulliken[13] on butadiene and the somewhat more empirical but more securely

TABLE 3. CALCULATED POLAR ENERGIES OF BONDS INVOLVING HYBRID σ CARBON ORBITALS

Electronegativity differences[a]	Polar energies Γ[b] (kcal/mole)
$x_{t_2} - x_H = 0{\cdot}39$	$3{\cdot}7 = \Gamma_{1H}$
$x_{t_1} - x_H = 0{\cdot}67$	$10{\cdot}4;\ \Gamma_{2H} - \Gamma_{1H} = 6{\cdot}7$
$x_{d_2} - x_H = 1{\cdot}22$	$34;\ \Gamma_{3H} - \Gamma_{1H} = 30$
$x_{t_1} - x_{t_2} = 0{\cdot}28$	$1{\cdot}8 = \Gamma_{12}$
$x_{d_2} - x_{t_1} = 0{\cdot}55$	$6{\cdot}9 = \Gamma_{23}$
$x_{d_2} - x_{t_2} = 0{\cdot}83$	$15{\cdot}9 = \Gamma_{13}$

[a] Using Mulliken's electronegativity scale (ref. 18), multiplied by a suitable factor to reduce the x's to Pauling's thermal scale.
[b] Γ values from equation (10), using a value of γ based on Pauling's work.

based calculations by the Pariser–Parr and similar methods are in close agreement with each other as to wave functions and bond orders. This agreement justifies placing considerable confidence in the values computed by Mulliken and Parr[17] (since they were based on the results of Parr and Mulliken on butadiene, and on similar results for benzene) for the vertical delocalization energies of butadiene and benzene. In other words, perhaps these purely theoretical quantities are more to be trusted than the empirical Δ's. It is noteworthy also that, after deducting estimated compression energies, these theoretical quantities are rather close to the empirical Δ's, giving some support to the belief that, in double-bonded systems at least, the empirical Δ's are really by good luck approximately equal to π-electron resonance energies. (It is only in triple-bonded systems that really *large* polar anomalies in the Δ's would be anticipated.)

Whatever may be the final conclusions as to the interpretation of Δ values, the work of Dewar and Schmeising has made it fairly certain that "natural" C—C bond lengths are somewhat shorter than hitherto supposed, when trigonal or digonal carbon σ AO's are involved. This means that, in correcting theoretically computed vertical delocalization energies to allow for compression energies, the latter will often be considerably smaller than hitherto estimated. Existing comparisons between theory and experiment will need some revision on this account, and particularly so in the case of semi-empirical computations on hyperconjugation. With reference to the latter, the uncertainties discussed above in the interpretation of empirical Δ's will need particular attention. It would be highly desirable that some hyperconjugation computations based on Pariser–Parr or SCF–LCAO methods be made. Nevertheless, there are a number of indications that recent computed values of π-delocalization energies in hyperconjugation are not very far wrong.

Rotation barriers and π bond energies

The safest way to determine an empirical value of the bond energy of a π bond would seem to be from the energy required to twist it through 90°, with, however, the following corrections:

(1) *add* the π-electron hyperconjugation energy of the twisted bond;

(2) *add* the energy of decompression of the bond, which should stretch considerably when the π bond is largely destroyed;

(3) correct for any barrier energy which would be associated with twisting through 90° in the absence of any π bonding. For C_2H_4 the energy required for a 90° twist is $61{\cdot}3 \pm 1{\cdot}2$ kcal (2·66 eV).[19] Roothaan and Mulliken[20] have computed the (vertical) hyperconjugation energy of 90° twisted ethylene to be about 1 eV, but for the somewhat stretched bond this may be, say, 0·8 eV. If R for the twisted bond is, say, 1·42 Å, the decompression correction, if the natural C^{tr}—C^{tr} length is 1·51 Å, may be 0·3 eV, while correction (3) may be, perhaps, −0·15 eV. The total (which of course is rather rough) is 3·6 eV.

For 1:3-butadiene one has a careful determination by Aston and collaborators[21] of the barrier height for a 90° twist of 1:3-butadiene, whose stable form is *s-trans*,[22] about the C—C single bond; their value is 5 kcal. Before setting up a theoretical counterpart, it is necessary first to recognize that in the absence of any π-electron (i.e. π_z-electron) delocalization there would be, (1), a considerable π-electron (i.e. π_z-electron) nonbonded repulsion across the C—C bond and further (2), an approximately equal π_y-electron nonbonded repulsion; also that, (3), on twisting, the sum of these two nonbonded repulsions (also the σ-electron nonbonded repulsions) should remain invariant according to usual VB theory (except for slight decreases in H—H interactions). The effect of π_z delocalization in butadiene must be viewed against this background. The vertical π_z delocalization energy (which, be it noted, depends on the delocalization-produced changes in *all* the bonds, not just in the C—C bond), as computed by Mulliken and Parr,[17] is 6·5 kcal. On twisting through 90°, this π_z-delocalization energy should be destroyed. It thus plays the same role here as the total π_z bond energy in ethylene. Also, just as in ethylene, hyperconjugation in the 90° twisted form restores some of the lost π-electron delocalization energy. Finally, there is a small correction for decompression of the σ bond on twisting. To estimate the total height of the barrier for 90° twisting, one may add to Mulliken and Parr's 6·5 kcal an estimated 0·9 kcal for second-order π_y hyperconjugation[23] in planar butadiene and then subtract an estimated 3·2 kcal for π_z and π_y first-order hyperconjugation[13] in 90°-twisted butadiene and 0·3 kcal for decompression, leaving 4 kcal for the net barrier height. If lack of complete invariance to rotation around a π-delocalization-free C—C single bond adds 1 kcal to the barrier, the result agrees with Aston's empirical barrier height of 5 kcal.

This agreement is consistent with the idea that the typical stability of planar forms in conjugated systems, and the corresponding stabilities of conjugated double bonds toward twisting, are due to π_z-electron delocalization. However, Dewar suggests that, since we do not understand the rather considerable barrier (3 kcal) toward rotation in ethane (where the same sort of nonbonded π_z and π_y repulsions should exist as discussed above for butadiene,[24] and with their sum invariant to rotation—but

[19] J. E. Douglas, B. S. Rabinovitch and F. S. Looney, *J. Chem. Phys.* **20**, 1807 (1952); **23**, 315 (1955).

[20] C. J. Roothaan and R. S. Mulliken, *Chem. Rev.* **41**, 219 (1947). The value 1 eV corresponds to $\beta_{CH} = 2\beta_{CC}$, $\delta = 0$, $\beta_{CC} = -3$ eV.

[21] J. G. Aston, G. Szasz, H. W. Woolley and F. C. Brickwedde, *J. Chem. Phys.* **14**, 67 (1946). See also C. M. Richards and J. R. Nielsen, *J. Opt. Soc. Amer.* **40**, 438 (1950), who say that certain frequencies estimated by Aston *et al* "have been examined critically and found essentially correct."

[22] Not only the vibrational spectrum, but also the intensity relations in the ultraviolet absorption spectrum, give assurance that 1:3-butadiene in liquid or solution is at least very predominantly in the *s-trans* form at room temperature.

[23] Based on A. Lofthus' estimates [*J. Amer. Chem. Soc.* **79**, 24 (1957)] of the π delocalization energies for hyperconjugation in similar situations.

[24] The variation of the intergroup H—H nonbonded repulsions in ethane on rotation cannot reasonably be large enough to account for the observed barrier.

VOL. 6 1959

weaker than in butadiene because of the greater C—C distance), a barrier of similar origin and comparable (or larger) magnitude might exist in butadiene. On the other hand, the theory in its present state gives a reasonable explanation of what is observed, and is not contradicted by anything which is observed; so why borrow trouble?

Something should be added about diphenyl, which apparently is *not* planar (except in the crystal). This can be attributed to the fact that two pairs of H atoms on the two phenyl groups are rather close together and presumably exert local nonbonded repulsions which overcome the π-electron delocalization forces favoring planarity. It is of interest that the nearest H—H distances in planar diphenyl (1·80 Å) are the same as for the two adjacent H atoms in the *cis* form of planar butadiene (the *cis* perhaps also is twisted; at any rate it is less stable than the *trans* form,[21] very likely at least partly for this reason). Even more interesting is the fact that these distances are practically the same as those (1·78 Å) between H atoms in CH_4, or adjacent H atoms in C_2H_6. The computed overlap integrals between two H atom 1*s* orbitals at this distance are remarkably large (0·28) at 1·78 Å[25], and one might reasonably expect large nonbonded repulsions between two such H atoms (of the order of $\frac{1}{2}$ eV energy, half the binding energy of two *bonded* H atoms in H_2 at the same distance apart).* The observed twist in diphenyl is not then surprising.

Dipole Moments and Other Properties

The factors determining dipole moments in conjugated and hyperconjugated systems are so complicated that great caution is required in drawing structural conclusions from observed moments. One must include not only primary contributions qR due to transfers of σ or π charge from a substituent to an adjacent unsaturated atom, but also covalent-dipole contributions whenever the transfer is between adjacent atoms whose participating orbitals are of unequal size, and also lone-pair dipole contributions in case hybrid lone-pair orbitals are present on substituent atoms. One must also include inductive contributions, both in the σ-electron system and in the π-electron system, especially the latter. Further, π-electron resonance should in general contribute. Finally, as Dewar and others have emphasized, one must take account of the fact that C—H or in general C—X σ bond moments must differ for C atoms with σ orbitals in different hybrid states, and that C—C σ bonds should have moments if their σ orbitals differ in hybrid state. In view of all this, one is inclined to agree with Dewar that the usual arguments for π-electron resonance as the cause of observed effects in conjugated systems are at present inconclusive. For example, it is incautious to conclude that resonance is responsible for the fact that the moments of are smaller than for CH_3X when X is more electronegative than carbon (more precisely, when the X σ bond orbital is more electronegative than a tetrahedral σ bond orbital of carbon).

However, a rough estimation of the effects of all the various modifying factors

* In C_2H_6, the overlap integral at nearest approach (2·31 Å) between H atoms in the two methyl groups is 0·15, which by an estimate similar to that just mentioned would correspond to a nonbonded repulsion of 0·1 eV: not large enough, incidentally, to account for the observed barrier to free rotation in C_2H_6.

[25] R. S. Mulliken, *J. Amer. Chem. Soc.* **72**, 4500 (1950).

mentioned above, except π-electron resonance, indicates that they may approximately cancel out as between C_6H_5X and CH_3X or perhaps even tend to *increase* the moment somewhat for —X, so that in the writer's opinion the usual conclusions could probably be justified by calculations taking all factors into account. But even if one agrees with Dewar that the usual arguments are not conclusive as they stand, one must concede that any argument that the observed effects are due solely to differences in hybrid states of carbon σ orbitals, and not to any appreciable extent to π-electron resonance is at least equally inconclusive. To be sure, Petro[27] has shown that the observed moments of conjugated and hyperconjugated systems can be explained quite well formally in terms of a set of bond moments differing for each different C—H and C—C hybrid σ case and assuming no contributions from conjugation or hyperconjugation. But the agreements obtained are no more conclusive than those obtained when contributions due to varying hybrid carbon orbitals are ignored and all effects associated with conjugation are attributed to π-electron resonance.

In view of the difficulty at the present time of correctly evaluating all relevant factors affecting dipole moments, it seems to the writer that one may place considerable reliance on theoretical calculations by the LCAO–SCF or Pariser–Parr or similar methods as giving approximately correct pictures of the effects of π-electron resonance on π-electron charge distributions in conjugated systems (compare paragraphs above on "Possible Usefulness of Theory"). However, more careful attention than hitherto should probably be given to the detailed interaction of σ-electron charge distributions on π-electron distributions.

In spite of what has been said about the difficulties of predicting bond moments, there do exist certain systems like azulene and the fulvenes where all carbon σ orbitals are "trigonal" so that C—H and C—C σ moments should cancel out, but π-electron resonance of the ordinary (sacrifical) conjugative type predicts dipole moments in agreement with observation. A similar situation exists for hyperconjugation in *cyclo*pentadiene. These cases are discussed in a separate paper.[7]

As to whether the observed dipole moments of such molecules as propylene, toluene, and methylacetylene are due to hyperconjugation, the writer believes, in accordance with remarks above about the usefulness of theory, that the most likely correct answer is "partly". In existing theoretical computations by the semiempirical LCAO–MO method, the extent and nature of hyperconjugation in such systems are determined by resonance paraments β (for the C—C π bonds) and β^* (for the C—H quasi-π bonds) and δ (the electronegativity of the H quasi-π orbitals relative to the carbon π orbitals): cf. Section II (e) of ref. 7. The now usually favored value of δ (about $-0{\cdot}5\beta$) is based on Coulson and Crawford's attribution of the dipole moment of toluene to hyperconjugation alone,[27] ignoring σ hybridization effects. The value of δ affects the computed hyperconjugation energy (the latter is considerably larger for $\delta = -0{\cdot}50\beta$ than for $\delta = 0$), and especially the charge distribution. It is clear that existing computations on hyperconjugation by the semiempirical method should be reviewed with respect to the best choice of δ.

If possible, the contributions of hybridization differences to observed dipole

[26] A. J. Petro, *J. Amer. Chem. Soc.* **80**, 4230 (1958).
[27] C. A. Coulson and V. A. Crawford, *J. Chem. Soc.* 2052 (1953).

moments should first be calculated, but this may be difficult. However, it seems not unlikely on the basis of a rough estimation that these contributions are smaller than the observed moments but in the same direction, so that hybridization and hyperconjugation could share in explaining the observed dipole moments. This would make δ/β still negative but smaller than 0·5. From LCAO–MO theory a negative value of δ/β is understandable[28] but somewhat accidental. It should be pointed out that hyperconjugation would still be present if δ/β were zero, or positive, but its contribution *to the dipole moment* would then be zero, or reversed in sign. In other words, a dipole moment is not an essential inherent characteristic of ordinary hyperconjugation (although it is for dative isovalent hyperconjugation).

VOL. 6 1959

Turning to other types of information, nuclear magnetic resonance, although some authors have disagreed,[26] seems to give clear evidence for π-electron resonance effects in conjugation and hyperconjugation.[29,30] Particularly convincing is Taft's discussion[29] of Gutowsky's data on *m* and *p*-substituted fluorobenzenes. The fluortoluenes indicate that the CH_3 group produces a hyperconjugative resonance effect similar in magnitude and sign to the conjugative resonance effect of Cl or Br, and thus confirms the negative sign of δ/β.

Strong experimental evidence for some important effects of hyperconjugation, predicted from semiempirical π-electron resonance theory, in the ultraviolet absorption spectrum of ethylene (relevant to the ground state of $C_2H_4^+$) was discussed in an earlier paper.[7] While in that case incipient isovalent, rather than ordinary sacrificial, hyperconjugation is involved, the fact that the effects were predicted using the same β and β^* parameters as in the usual semiempirical calculations on ordinary hyperconjugation supports the approximate correctness of the latter's predictions.

Dewar's argument (4) in the Introduction as to the irrelevance of the electronic spectra of hyperconjugated, and a similar argument for conjugated, systems can be answered as follows: the same LCAO–MO theory which approximately reproduces the observed excited state effects can be trusted in its predictions about ground state characteristics.

Dewar's argument (5) is certainly valid, but it is not an argument *against* π-electron resonance in ground states. It is of interest that Taft finds strong evidence for a close parallelism between activated and ground state properties in his comparison[29] of reactivity parameters with nuclear magnetic shielding parameters in substituted fluorbenzenes. Activated states, as noted in the companion paper[7], probably often involve isovalent conjugation or hyperconjugation in incipient carbonium ion structures.

An interesting ground state property which shows great sensitivity to conjugation is polarizability, as shown in the intensities of Raman lines.[31] This is in agreement with what is expected from π-electron resonance theory. One might, however, perhaps argue that polarizability is not a proper ground state property, since the theory makes it dependent on the strengths and frequencies in the electronic absorption spectrum of the molecule, it being the latter which, in agreement with π-electron theory, shows great changes in conjugation.

[28] N. Muller, L. W. Pickett, and R. S. Mulliken, *J. Amer. Chem. Soc.* **76**, 4770 (1954); Y. I'Haya, *J. Chem. Phys.* **23**, 1165 (1955).
[29] R. W. Taft, Jr., *J. Amer. Chem. Soc.* **79**, 1045 (1957); R. W. Taft Jr. and I. C. Lewis, Report at Conference on Hyperconjugation, Bloomington, Indiana, June, 1958. *Tetrahedron* **5**, 210 (1959).
[30] R. A. Hoffman, *Molecular Phys.* **1**, 326 (1958).
[31] Private communication from W. T. Alexanjan, *U.S.S.R. Academy of Sciences* Moscow.

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PRELIMINARY COMMUNICATION

The reaction of dichlorocarbene with secondary amines

(*Received* 23 *December* 1958)

THE intermediacy of dichlorocarbene in the formation of isocyanides from primary amines in the presence of aqueous base and chloroform was first suggested by Nef[1] and later by Hine.[2] We wish to report that secondary amines react to give the derived formamide under conditions which have been demonstrated[3] to involve dichlorocarbene as an intermediate. When chloroform is added to a stirred mixture of the amine, benzene; and potassium *tert.*-butylate maintained at 5°, an exothermic reaction takes place to give, after work up, the corresponding amide. Thus, diethylamine, dimethylamine, diphenylamine and piperidine react to give diethylformamide, dimethylformamide, diphenylformamide, and N-formylpiperidine, respectively. The amides were identified by comparing the infrared absorption spectra with those of the authentic materials. Yields varied from less than 1–31 per cent. The poorer yields were obtained in earlier experiments and may be improved by more recent refinements in experimental technique.

We believe that this reaction proceeds by an attack of dichlorocarbene on the amine with the expected dichloromethylamine intermediate proceeding to the observed amide product under the conditions of the reaction and work up. It seems unlikely that the reaction involves a displacement on chloroform by the dialkylamide anion since chloroform would not be expected to exist very long in the medium used. When aqueous sodium formate and the amine are placed together under the reaction conditions no amide is formed. Thus the trivial explanation, involving prior basic hydrolysis of chloroform to the formic acid salt, followed by reaction with the amine to give the amide, is ruled out.

Smith[4] recently reported the formation of a small amount of 3-diethylaminopropylformamide in the attempted preparation of the isocyanide from 3-diethylaminopropylamine by treatment with chloroform and base. He suggests an attack of dichlorocarbene on the amine to give the structure R-NH-CHCl, which then hydrolyzed to give the observed product.

We have also found that the tertiary amine, benzyldimethylamine, reacts under the conditions described above to give a small yield of dimethylphenylacetamide, m.p. 39–40°, mixed m.p. with authentic dimethylphenylacetamide, 39–40°. The infrared spectrum of the product was identical to that of authentic dimethylphenylacetamide. We believe that this product arises through a Stevens rearrangement of the nitrogen ylid formed by the addition of dichlorocarbene to the amine. Migration of a benzyl group in such a manner, followed by hydrolysis, could explain the observed product. The reaction also produced dibenzyl, identified by m.p., infrared spectrum, nuclear magnetic resonance spectrum; and other, as yet unidentified products.

Stevens and Bamford[5] have shown that when diazofluorene is irradiated in the presence of benzyldimethylamine a considerable quantity of 9-benzyl-9-dimethylaminofluorene is produced. These authors explain the product by postulating a migration of the benzyl group in the nitrogen ylid intermediate formed from the addition of the carbene to the amine.

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[1] J. U. Nef, *Liebigs Ann.* **298,** 202 (1897).
[2] J. Hine, *J. Amer. Chem. Soc.* **72,** 2438 (1950).
[3] W. Doering and A. K. Hoffman, *J. Amer. Chem. Soc.* **76,** 6162 (1954).
[4] P. A. S. Smith and N. W. Kalenda, *J. Org. Chem.* **23,** 1599 (1958).
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NOTES

VOL.
6
1959

Lochnericine—A new alkaloid from *Lochnera rosea*

(*Received* 1 *December* 1958)

THIS paper reports the isolation of a new alkaloid, Lochnericine, from the root bark of *Lochnera* (Vinca) *rosea*, from which alkaloids of the Rauwolfia type have previously been isolated.[1–6]

Lochnericine has the molecular formula $C_{21}H_{24}$ or $_{26}N_2O_3$ and contains one OCH_3 group as ester and one C—CH_3 group. The ultra-violet spectrum in alcohol shows maxima at 227 mμ (log ε 4·10), 299 mμ (log ε 4·15) and 328 mμ (log ε 4·32) and minima at 214, 258 and 306 mμ. The infra-red spectrum shows medium absorptions at 2·96 μ, 3·39 μ, (free >NH or —OH group?) and C—H. absorption at 3·57 μ. An ester group is definitely indicated by strong absorptions at 5·98 μ and 6·21 μ and is supported by hydrolytic evidence. Indole nucleus appears to be indicated by strong absorptions at 6·21 μ and 6·80 μ.

Lochnericine gives only a very slight blue-violet colouration with Keller reagent unlike the β-carboline serpentina bases. It gives a green colour with concentrated nitric acid, and no colour with concentrated sulphuric acid. Erdmann's reagent gives a persistent intense prussian blue colour.

The melting point, U.V. and I.R. data and colour reactions suggest that it is a new alkaloid.

EXPERIMENTAL

The dry root bark (6 kilos) was percolated repeatedly with cold methanol, evaporated at 100 mm to 1 l., and shaken out with petroleum-ether b.p. 60–80° (5 l.). The volume was reduced to 100 ml, cooled and extracted with 5% HCl (900 ml). The clear aqueous portion was made ammoniacal (pH just above 7) and the curdy light yellow precipitate filtered (3·5 g), washed well with a little ice-cold 50% methanol to remove colouring matter. The residue was crystallised repeatedly, first from petroleum ether, then from ethanol, and finally from methanol. Lochnericine (0·5 g), long, prismatic rods from all three solvents, m.p. 188–189° was obtained, yield 0·008% on dry root bark.

Chromatography of lochnericine 0·1 g was done by the method of "Divided columns"[7] (10 g Mercks' chromatographic alumina, 3 columns, length of each column 8 cm and diameter 7 mm). On elution with absolute alcohol, all the lochnericine was obtained in fractions 2, 3 and 4 (15 ml each). The melting point of the residue before and after crystallisation was 188–189°.

$$[\alpha]_D^{16^\circ} = -36{\cdot}1 \text{ (}c\text{, 12·47 in alcohol.)}$$

Paper-strip chromatography (ascending type) with *n*-butanol: hydrochloric acid: water: 100 : 4 : 30 showed a single dull violet band under U.V. light with an average *Rf* of 0·94. (Found: C, 71·7, 71·3; H, 7·4, 6·8; O, 13·6, 13·6; N, 8·3, 7·8, OCH_3, 9·3; CCH_3, 3·7 active H, 0·51, 0·52, Calc. for

[1] R. A. Paris and H. Moyse Mignon, *C.R. Acad. Sci., Paris* **236**, 1993 (1953).
[2] A. Chatterjee and S. K. Talapatra, *Sci. Cult.* **20**, 568 (1955).
[3] P. P. Pillay, T. N. Santhakumari and C. P. N. Nair, *Bull. Res. Inst. Univ. Kerala* V, No. 1. 65 (1957).
[4] W. B. Mors, P. Zaltzman, J. J. Beerboom, S. C. Pakrashi and C. Djerassi *Chem. & Ind.* 173 (1956).
[5] M. M. Janot and J. Le Men, *C.R. Acad. Sci., Paris* **243**, 1789 (1956).
[6] N. K. Basu and B. Sarkar, *Nature, Lond.* **181**, 552 (1958).
[7] P. P. Pillay, D. S. Rao, C. P. N. Nair and E. T. Varkey, *Chem. & Ind.* 258 (1958).

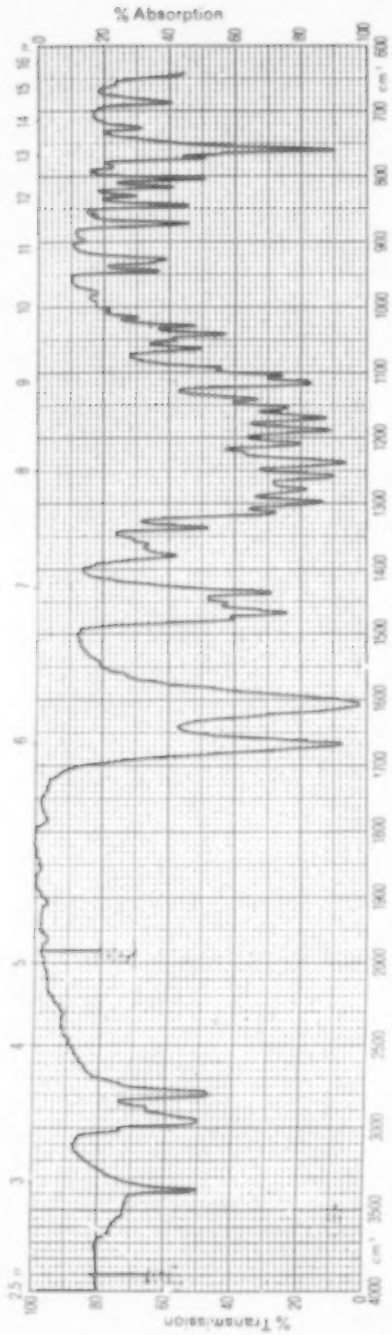

FIG. 1. Infra-red spectrum of "Lochnericine". Medium: KBr.

$C_{21}H_{24}N_2O_8$; C, 71·58; H, 6·82; O, 13·64; N, 7·95; one OCH_3 8·8%; one CCH_3 4·3%; two active H, 0·57. Calc. for $C_{21}H_{26}N_2O_8$: C, 71·19; H, 7·32; O, 13·56; N, 7·91; one OCH_3 8·7%; one CCH_3 4·2; two active H, 0·56%).

Hydrolysis of Lochnericine. Lochnericine (11 mg) and 10% alcoholic sodium hydroxide (0·6 ml) was sealed and heated in the water-bath for 30 min. The deep orange yellow solution on careful additions of sulphuric acid gave at the isoelectric point of about 7 pH, a sparingly soluble yellowish brown amorphous solid, soluble in and forming salts with acids and alkalies.

Acknowledgement—For the analytical results, U.V. and I.R. spectra we are indebted to Dr. A. Hofmann, Vize Direktor Der Sandoz A.G. Basel, Switzerland.

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A novel trans-glycosylation reaction

(*Received* 12 *December* 1958)

The replacement of one aglycone in an O- or N-glycoside by another aglycone has been variously termed 'transglycosidation'[1] or 'transglycosylation'.[2,3] Such a process has been found to occur only with difficulty when one O-aglycone replaces another,[1] but proceeds readily under mildly acidic conditions for the replacement of one N-aryl group by another in the N-aryl-glycosylamines.[2,3] So far no case has been recorded of the replacement of an O-aglycone by a N-aglycone. In the course of an investigation of some colour reactions of arylamines and sugars, we have noted such a replacement, and shown that in certain cases it may proceed readily under mildly acidic conditions. Treatment of methyl-glucofuranoside (I, R = CH_3) with *p*-nitroaniline in anhydrous methanol containing 0·01 to 0·1 mol of hydrogen chloride, leads to rapid formation of a mixed O- and N-glycoside (II, R = CH_3; R′ = $pNO_2{\cdot}C_6H_4$) which on prolonged treatment yields the N-*p*-nitrophenyl-D-glucosylamine (III, R′ = $pNO_2{\cdot}C_6H_4$).

Similarly *p*-chloroaniline under the same conditions reacts with methyl-glucofuranoside to yield a compound II, (R = CH_3:R′ = $pCl{\cdot}C_6H_4$). In contrast methyl-α-D-glucopyranoside was recovered unchanged even on prolonged boiling under these conditions. Similar results were observed with the ethyl- and *n*-propyl- glucosides, and with the corresponding galactose compounds.

When methyl-3:6-anhydro-α-D-glucopyranoside was added to a methanolic solution of *p*-nitroaniline or *p*-chloroaniline containing catalytic proportions of hydrochloric acid, a similar reaction occurred.

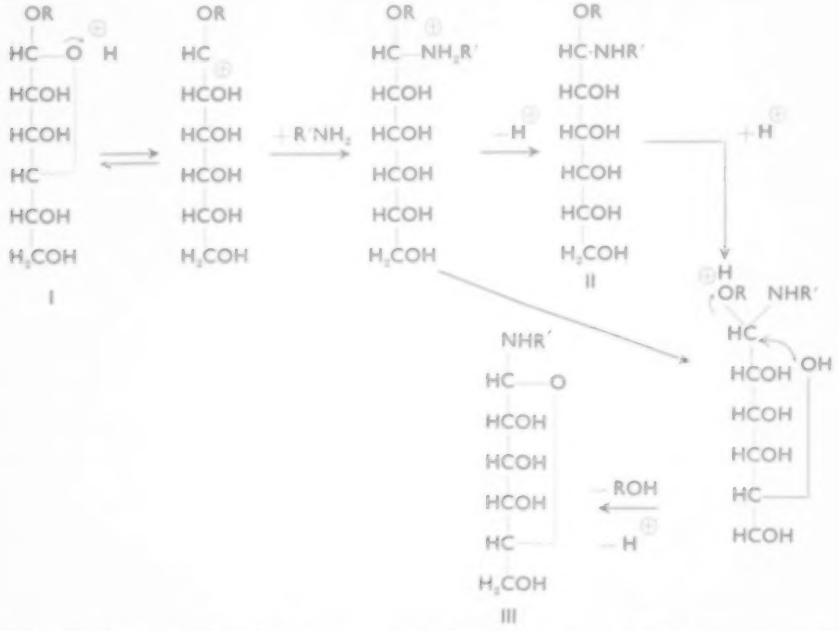
[1] W. Pigman and R. O. Laffre, *J. Amer. Chem. Soc.* **73**, 4994 (1951).
[2] R. Bognar and P. Nanasi, *Nature, Lond.* **171**, 475 (1953).
[2(a)] R. Bognar and P. Nanasi, *J. Chem. Soc.* 189 (1955); [3] W. G. Overend and J. B. Lee, unpublished observations.

It would appear that reaction only occurs readily when the labile furanose ring is present, or when the (usually stable) pyranose ring system is rendered labile[4] as in the bridged ring system of the 3:6-anhydro-glycosides. As the reaction proceeds readily in anhydrous conditions it cannot involve hydrolysis and recombination.

The isolation of compounds of type II, suggests that these may be formed intermediately in the conversion of the O-glycoside (I) to the, normally pyranose,[5] N-aryl-glycosylamine. Proton addition to the ring oxygen, yielding a [C(1)] carbonium ion to which the amine may then add, the charged product expelling a proton, or upon prolonged treatment eliminating the O-alkyl group, is suggested, as illustrated below.

The well-known conversion of methyl-3:6-anhydro-glucopyranosides to the furanose form, and of the corresponding galactose compound to the open chain form, proceeds readily under anhydrous conditions,[4] suggesting an analogous intermediate carbonium ion formation with which, in the presence of an arylamine, formation of an N-aryl-glycosylamine occurs. Alternatively the protonated arylamine may react directly with the O-glycoside.

This study has not been extended to include more basic arylamines: these may react less readily as studies have shown[3,5] that the arylamine–hexose bond becomes weaker with increasing basicity of the amine.



Solutions of amine hydrochlorides, particularly the nitro-anilines, are useful spray reagents for paper chromatographic detection of alkyl-O-glycofuranosides and alkyl-3:6-anhydro-O-glycosides, rapidly yielding coloured spots at room temperature thus readily differentiating these compounds from the corresponding alkyl-O-glycopyranosides which yield spots only very slowly (ca. 24 hr) under the same conditions. The basis of these colour reactions would appear therefore to depend upon the primary formation of the glycosylamine, followed possibly by rearrangements of the type reported by Amadon.[6]

EXPERIMENTAL

1-O-*Methyl*-N-p-*chlorophenyl*-D-*aldehydo-glucosylamine*. *p*-Chloro-aniline (0·8 g) and methanolic hydrogen chloride (1 drop, 17%) were added to a hot methanolic solution of methyl α-D-glucofuranoside, (0·92 g). After 5 min the solution was cooled, neutralised (barium carbonate), filtered and

[4] W. Haworth, N. Owen and F. Smith, *J. Chem. Soc.* 88, (1941).
[5] J. Honeyman and A. R. Tatchell, *J. Chem. Soc.* 967 (1950).
[6] N. Amadon, *Atti. Acad. Lincei* [6], **2**, 337 (1925); **13**, 72 (1931).

evaporated to dryness at the pump. Extraction of the residue with hot methanol yielded a solution of 1-O-methyl-N-*p*-chlorophenyl-D-aldehydoglucosylamine (II: $R' = p\text{Cl}\cdot C_6H_4$. $R = CH_2$), deposited on cooling as white cubes, m.p. 145°, $[\alpha]_D^{16}$ +85° (*c* 0·165 in pyridine). (Found: C, 48·0, H, 5·9, N, 4·3; $C_{13}H_{20}O_6NCl$ requires: C, 48·5, H, 6·2, N, 4·3%).

1-O-*Methyl*-N-p-*nitrophenyl*-D-*aldehydoglucosylamine*. *p*-Nitro-aniline (1·5 g) and hydrochloric acid (30%, one drop) were added to a hot methanolic solution (15 ml) of methyl α-D-glucofuranose (1·4 g) and the clear solution allowed to cool. Bright yellow needles were deposited. Recrystallisation from methanol yielded 1-O-methyl-N-*p*-nitrophenyl-D-aldehydo-glucosylamine, (II: $R' = p\cdot NO_2\cdot C_6H_4$. $R = CH_2$), m.p. 162–3°, $[\alpha]_D^{16}$ +46° (*c* 0·228 in pyridine). (Found: C, 44·4; H, 5·9; N, 7·1; $C_{12}H_{20}N_2O_8\cdot H_2O$. Requires: C, 44·6; H, 6·2; N, 8·0%).

(a) Methyl α-D-glucopyranoside (2·0 g) was treated with *p*-chloroaniline in methanol containing hydrogen chloride (3 drops, 17%). The mixture was refluxed (20 min). On cooling methyl α-D-glucopyranoside (1·1 g m.p., and m.p. on admixture with an authentic sample, 164·5–165°) separated. A further portion (0·6 g, m.p. 163–165°) was recovered from the mother liquor. Unchanged material also was recovered using *p*-nitroaniline in place of *p*-chloroaniline under the same conditions.

Under the above conditions ethyl β- and α-D-glucofuranosides yielded, with *p*-nitroaniline, N-*p*-nitrophenyl-D-glucosylamine, m.p. 183–185°, $[\alpha]_D^{22}$ −190° (*c* 1·1 in pyridine). Bognar[3(a)] reports m.p. 185°, $[\alpha]_D$ −193° (*c* 1·3 in pyridine). Similarly *n*-propyl-D-glucofuranose (α:β mixture) yielded a product m.p. 180°, giving no depression on admixture with an authentic sample. This compound yielded a tetra-acetate, yellow needles m.p. 168°, $[\alpha]_D^{18}$ −77·5° (*c* 0·109 in pyridine). (Found: C, 51·5; H, 4·5; N, 5·9; $C_{20}H_{24}N_2O_{11}$. Requires: C, 51·3; H, 5·1; N, 6·0%).

A mixture of methyl-α- and β-D-galactofuranosides with *p*-nitroaniline under the above conditions yielded yellow needles, m.p. 200–201°, $[\alpha]_D^{18}$ −191° (*c* 2·0 in pyridine). Frerejacques[7] reports m.p. 203°, $[\alpha]_D$ −202°, for N-*p*-nitrophenyl-D-galactosylamine. Methyl-β-D-galactopyranoside did not react under the same conditions.

(b) Methyl-3:6-anhydro-α-D-glucopyranoside (0·7 g) was added to *p*-nitroaniline (1·2 g) in hot methanol containing a trace of hydrogen chloride. The solution upon slow evaporation deposited deep-red plates, recrystallised from methanol, (0·4 g), m.p. 141–143°, $[\alpha]_D^{18}$ −200° (*c* 0·8 in pyridine). (Found: C, 51·7; H, 4·3; $C_{18}H_{20}N_4O_8$. Requires: C, 51·4; H, 4·7%).

Acknowledgment—The authors wish to express their thanks to Professor W. Cocker for his interest in this work.

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[7] J. Frerejacques, *C. R. Acad. Sci., Paris* **207**, 638–640 (1938).

VOL. 6 1959

Tetrahedron, 1959, Vol. 6, pp. 94 to 96. Pergamon Press Ltd. Printed in Northern Ireland

BOOK REVIEWS

Methoden der Organischen Chemie (Houben-Weyl). Band I/1. Vierte, Völlig Neu Gestaltete Auflage. Unter Besonderer Mitwirkung von O. BAYER, Leverkusen, H. MEERWEIN, Marburg, and K. ZIEGLER, Mülheim. Allgemeine Laboratoriumspraxis. Edited by EUGEN MÜLLER, Tübingen. Georg Thieme Verlag, Stuttgart, 1958, xlii + 1049 pp., 18·5 × 26 cm, DM 198 (Subskriptionspreis DM 178.20).

FOR many years Houben-Weyl's *Methoden* was a reliable and much consulted source of guidance and reference for the practising organic chemist. Unfortunately the third edition of the work became sadly outdated and was being relegated to more and more remote shelves of our libraries. It is gratifying that since 1953 a greatly expanded and fully revised fourth edition has been appearing, of which the volume at hand is the most recent instalment.

Under the editorship of Prof. Eugen Müller, with an editorial board composed of Profs. Otto Bayer, Hans Meerwein and Karl Ziegler, eight volumes had been issued before the inception of *Tetrahedron*, dealing with analytical and physical methods, general chemical methods and with parts of the discussions devoted to compounds of nitrogen, of oxygen and of sulphur, selenium and tellurium. Since complete coverage of the literature is neither possible or desirable, the editorial policy adopted is to include only tried, reliable and significant procedures, necessitating critical selection from an abundance of material. This task is being accomplished with the aid of numerous colleagues, active in academic institutions as well as in industrial laboratories, from the files of which hitherto unpublished material has frequently been contributed.

The most recent half-volume is devoted to "General Laboratory Practice", from gram-scale preparative work to operations of pilot-plant size. This is particularly true of manipulations like filtration, pressing of filter cakes, solvent extraction, adsorption, drying, distillation and centrifugation. The specific pieces of equipment referred to are, not surprisingly, of preponderantly German or European manufacture. The second half-volume will cover *inter alia*, micro-preparative methods and vacuum work.

A further distinguishing feature of the present treatise is the inclusion of several chapters dealing essentially with laboratory craft: glasses and their properties; assembly of glass apparatus; the use of ceramics, plastics and metals in the laboratory; cements and glues; general notes on laboratory planning.

Space does not permit reference to all of the subjects covered, but mention will be made of chapters that seemed to have particular interest. A. Lüttringhaus's contribution on "Crystallization" endeavors to present in systematic form the manifold methods and tricks by which chemists have coaxed molecules to arrange themselves in the orderly fashion of a lattice. A unique presentation of the use of inclusion compounds is given by W. Schlenck, and a chapter by F. Cramer and O. Bayer on the use of complexes and molecular compounds will be welcomed by many. G. Hesse has dealt with chromatography and K. Bratzler with gas adsorption. Gas chromatography has advisedly been omitted, until "its development for preparative purposes has been achieved." Ion exchange is treated in an extensive chapter by R. Griessbach and S. Naumann, and the more recently developed redox resins are discussed by A. Manecke. A thorough discussion of extraction and multiplicative distribution in columns or batches is given by O. Jübermann. Electrophoresis in its preparative aspects is described by W. Grassmann and K. Hannig.

Throughout the work, the theoretical principles for each method are clearly set forth to enable the reader intelligently to apply the practical examples to his own problems.

Physical appearance and typography are of a high calibre. Older chemists will welcome the resumption of a great tradition and younger colleagues will surely benefit from becoming acquainted with this thorough and authoritative treatise.

HANS HEYMANN

Experientia Supplementum VII. XVIth International Congress of Pure and Applied Chemistry. (Paris, 18–24, VII, 1957. Main Congress Lectures.) Birkhäuser Verlag, Basel, Switzerland, 1957. 355 pp., 36.0 Sw. Fr.

VOL. 6 1959

THIS book brings together the texts of the main lectures delivered at the 16th International Congress of Pure and Applied Chemistry held in Paris in July, 1957. Each lecture is printed in the language in which it was delivered, seven each in English and French and four in German.

The Centenary Lecture of the "*Société chimique de France*" delivered by Sir Cyril Hinshelwood, entitled "*Réflexions sur la cinétique chimique*" appears first, followed by the Inaugural Lecture by G. Natta called "*Catalyse stéréospécifique et polymères stéréo-isomériques. Preparation de fibres, matières plastiques et élastomères nouveaux*". This lecture by Professor Natta occupies some 39 pages and gives an excellent account of the variations that can be effected in the polymerisation processes of the α-olefines, a subject to which he has made such a great contribution.

Then follow five lectures delivered to the Physical Chemistry Section. The lecture by Glenn T. Seaborg on the transuranium elements includes a dramatic account of the discovery of element 101, mendelevium, speculations on further transuranium elements and an outline of the heavy-ion linear accelerator at Berkeley. The text is illustrated by figures and three photographs, which give an idea of the immense size of the Berkeley accelerator. Altogether this lecture succeeds admirably in conveying the atmosphere in the Berkeley laboratory during the discovery of the new elements. Other lectures to this section are by R. G. W. Norish, R. M. Barrer, S. R. de Groot and C. Ouellet.

The lectures to the Inorganic Chemistry Section are by H. Haraldsen, E. Wiberg, A. G. Maddock, H. Nowotny and A. Wittmann, and an account by Leo Brewer of "High Temperature Chemistry. A Pioneering Field," which opens up a fascinating new field.

The Organic Chemistry Section contains the following lectures: V. Prelog, "*Untersuchungen von transanularen Eliminationen und Substitutionen mit Hilfe von Isotopen*"; P. D. Bartlett, "The Initiation of Organic Chain Reactions"; G. Wittig, "*Komplexbildung und Reaktivität in der metall-organischen Chemie*"; T. Nozoe, "Chemistry of Natural Tropolone and Allied Compounds"; L. Marion, "*Structure de quelques alcaloides du delphinium*"; and A. Terenin, "*Photoréactions électroniques des colorants organiques*", which is mainly concerned with the chlorophylls and other tetrapyrrol pigments.

The book is well produced and is pleasant to read. It is difficult, however, to know for whom it is intended, since the material it contains ranges over an enormous field and it would appear that most of the lecturers were reviewing their subjects rather than presenting new data or ideas. The value of these lectures as a starting point for further reading is rather variable, as some of the lecturers have provided no references to the original literature while others have given extensive lists. Perhaps such collections as this, written by authors from all over the world, are valuable, and the juxtaposition of lectures in English, French and German may stimulate English readers to try their hand at foreign languages; nevertheless one may perhaps question whether the present day passion for indiscriminately printing, in full, the proceedings of innumerable congresses, symposia and meetings of all sorts really serves the ends of science. It is doubtful if many individuals will feel that they must possess this volume, although it is certain that everyone will find one or two of the lectures most interesting.

S. P. DATTA

J. FERGUSON: **Bibliotheca Chemica,** Vol. 1. Derek Verschoyle Academic and Bibliographical Publications Ltd.; Pergamon Press Ltd., London, 1954. xxi + 487 pp., £5. 5s.

THIS unique book goes back to James Young (1811–1883), the Scottish industrial chemist whose discovery of the production of paraffin oil by distillation of Scotch bituminous shales made him a wealthy man. He established a library of early chemical works and after his death his family entrusted the cataloguing of the library to John Ferguson, Regius Professor of Chemistry in the University of Glasgow, and a distinguished historian of chemistry. The knowledge accumulated by Ferguson in many years of study of the writings of early chemists went to the making of this author catalogue

of Young's collection. It was published in 1906 in an edition limited to 250 copies paid for by Young's descendants; for at that time there was little interest in the history of chemistry in Britain. It proved to be the most important bibliography ever compiled in this field and became an indispensable reference for historians of chemistry. It is the only book of its kind to supply pagination and full titles of the items catalogued.

To the non-specialist the main attraction of the work lies in the pawky thumbnail biographies of authors. Of Gioseppe Francesco Borri (d. 1695), Ferguson says that he lived at Amsterdam "in great magnificance—upon his wits; when these were exhausted he departed to Hamburg." We are warned against confounding—as if one would—John Case (Johannes Casus) of Oxford (d. 1600) with Giovanni della Casa (d. 1557) of Benevento "who might have been a cardinal had not the church had a fit of the morals." Edward Kelley (1555–1595) of Worcester "was trained as an apothecary so that he had some familiarity with chemistry . . . He was an unscrupulous adventurer, not to say a thorough-going scoundrel. He was therefore a man of ability without any moral restraint."

These lives show much of the ups and downs of human fate. Georg Fikenscher (d. 1686) was in high favour at the court of Beyreuth for ten years because it appeared he could convert mercury into gold and silver—but he was eventually detected and executed—"While it was his intention to fix mercury, the result was just the opposite, for it was he who was in the fix."

In the Introduction we find Ferguson in another mood. Commenting on how alchemical theories have perished, he points out that those of the modern scientist will suffer the same fate: "Let not the modern student of science imagine that he and his work will escape the universal doom. His discoveries, his theories, the most recent, the most comprehensive and progressive, sooner or later will become mere archaeological data." Solemn but true.

The present edition is by a photo-lithographic process from the original Vol. I, which covers from A to K. The publishers have done the history of chemistry a great service in making this famous reference work widely available and the publication of the remainder of the catalogue will be eagerly awaited.

T. S. Wheeler

ERRATA

1. R. F. Hutton and F. H. Westheimer, *Tetrahedron* **3**, 73 (1958).
   The wording in line 30 on p. 76 should read "structure I" and not "structure II".
2. A. Heusner and K. Zeile, *Tetrahedron* **3**, 312 (1958).
   The arrow between formulae II and III should point from left to right.
   The first two words of the eighth line on p. 313 should read "vorstehende Mitteilung".
3. R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **4**, 256 (1958).
   p. 263, Table 3: the formula at the bottom of the column "Substituents", in the first part, of this table should have been centred between compounds "Pimpinellin" and "Psoralene".
   p. 268, Reference 43: this reference should read "*Tetrahedron* **3**, 230 (1958)".
   p. 269, Experimental Section: the second line in this section should refer to ref. 45, not 46 as shown.
4. "Papers to be published in future issues", *Tetrahedron* **5**, 103–104 & 354 (1959).
   The paper listed as "A. J. Birch, H. Smith and T. M. B. Wilson: The steric course of addition of some electrophiles to enolate anions derived from polycyclic systems" should not in fact have appeared. We apologise to the authors for any inconvenience caused by this oversight.

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VOL.
6
1959

CONDENSATION OF ISATIN WITH DIKETONES

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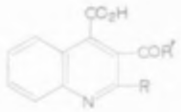
Abstract—The condensation of isatin with enolisable acyclic and alicylcic 1:3-diketones has been investigated and the structures of the acylated cinchoninic acids obtained have been determined. The condensation of acetonylacetone with potassium isatate is also described. Condensations of isatin with 1:3-*cyclo*hexadiones in neutral or acid media has been shown to give products different from those in alkaline condensation.

SEVERAL acyclic 1:3-diketones with a methylene group between two carbonyl groups undergo the Pfitzinger reaction[1,2,3] with isatin or isatic acid to yield the corresponding



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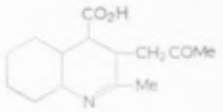


II

2-substituted-3-acylcinchoninic acids (a) R = R′ = Me; (b) R = Me, R′ = Et; (c) R = Me; R′ = Ph; (d) R = R′ = Ph.

Acetylacetone and isatin yield 2-methyl-3-acetyl-cinchoninic acid (Ia) the structure of which was established by (i) oxidation to 2-methyl-3:4-quinolinedicarboxylic acid,[4] (ii) decarboxylation to 3-acetylquinaldine,[5] (iii) heating with KOH to give quinaldine. The best yields of (Ia) (73%, 80%) were respectively obtained by carrying out the condensation in presence of KOH or by heating with anhydrous potassium isatate in absence of a solvent. Strong alkali hydrolysed acetylacetone to acetone which condensed with potassium isatate to give 2-methylcinchoninic acid.

2-Methyl-3-propionylcinchoninic acid (Ib) is obtained by condensing propionylacetone with anhydrous potassium isatate in absence of solvent. Only a resinous product is formed in strongly alkaline solution. The position of the Me group in (Ib) was determined by converting the acid into quinaldine. Anhydrous potassium isatate and benzoylacetone condense to give 2-methyl-3-benzoylcinchoninic acid (Ic), the structure of which was proved by decarboxylation to 3-benzoylquinaldine,[6] and degradation to quinaldine and benzoic acid. Under strongly alkaline conditions benzoylacetone gives acetophenone[7] which condenses with potassium isatate giving

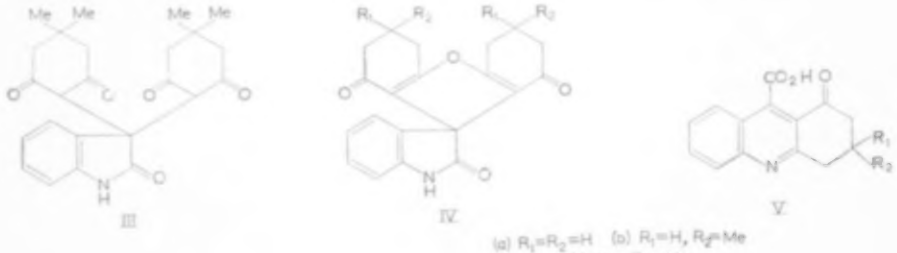
* Lj. Lorenc, PhD. dissertation.

[1] W. C. Sumpter, *Chem. Rev.* **34**, 393–434 (1944).
[2] W. Steinkopf and H. J. von Petersdorff, *Liebigs Ann.* **543**, 119 (1940) N.P. Buu-Hoï and R. Royer, *Bull. Soc. Chim. Fr.* 820 (1947); N.P. Buu-Hoï and R. Royer, *Rec. Trav. Chim.* **67**, 175 (1948); J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.* 393 (1955).
[3] E. Noelting and A. Herzbaum, *Ber.* **44**, 2585 (1911).
[4] V. M. Micović, *Bull. Soc. Chim. Fr.* **6**, 1156 (1939).
[5] J. Eliasberg and P. Friedländer, *Ber.* **25**, 1752 (1892); O. Stark, *Ibid.* **40**, 3425 (1907).
[6] O. Stark, *Ber.* **42**, 715 (1909).
[7] E. Fischer and C. Bülow, *Ber.* **18**, 2132 (1885); L. Claisen and O. Lowman, *Ber.* **21**, 1152 (1888); R. Connor and H. Adkins, *J. Amer. Chem. Soc.* **54**, 3420 (1932).

2-phenylcinchoninic acid. Dibenzoylmethane and anhydrous potassium isatate react to give 2-phenyl-3-benzoylcinchoninic acid (Id) (63%), and conversion of the acid to 2-phenyl-3-benzoylquinoline[6] and subsequently to 2-phenylquinoline established the structure of the acid.

Potassium isatate reacts with 1:4-diketones e.g. acetonylacetone giving 2-methyl-3-acetonylcinchoninic acid (II) which on treatment with KOH gives 2:3-dimethylquinoline.

Vorländer *et al.*[6] have shown that 1:3-*cyclo*hexanediones react with isatin in glacial acetic acid giving the corresponding substituted octahydroxanthenes (IV). It has now been found that 1:3-*cyclo*hexanedione and 5-methyl-1:3-*cyclo*hexanedione react under various conditions to give the corresponding octahydroxanthenes, (IVa and b) and 5:5-dimethyl-1:3-*cyclo*hexanedione (methone) reacts with isatin in ethanol or in absence of solvent yielding the alkali soluble 3:3-*bis*[5':5'-dimethyl-1':3'-dioxo-2'-*cyclo*hexyl]oxindole (III)[8], which is also readily obtained when isatin and methone are refluxed in aqueous ethanol containing KOH. In glacial acetic acid methone and isatin yield *spiro*[octahydro-3:3:6:6-tetramethyl-1:8-dioxoxanthene-9:3'-oxindole] (IVc). The cyclisation of (III) to (IVc) takes place readily in boiling glacial acetic acid. Condensation of anhydrous potassium isatate with one mole of 5-methyl- or 5:5-dimethyl-1:3-*cyclo*hexanedione takes a different course. In addition to (IVb) and (IVc) and (III), 3-substituted-1:2:3:4-tetrahydro-1-oxo-9-acridinecarboxylic acids (Vb) and (Vc) are obtained. The structure (V) is proposed for the acridinecarboxylic acids on the assumption that isatic acid reacts with the methylene group situated between the two keto groups of the 1:3-*cyclo*hexanedione in analogy with the reaction of open chain 1:3-diketones with isatic acid.



(a) $R_1=R_2=H$ (b) $R_1=H$, $R_2=Me$
(c) $R_1=R_2=Me$

In the condensation of 1:3- and 1:4-diketones with isatic acid under various conditions, the only procedure which gives satisfactory yields of 2:3-substituted cinchoninic acids (I, II, V) consists in heating the diketones with anhydrous potassium isatate in absence of solvent. Condensations in aqueous KOH (the usual conditions for Pfitzinger reaction) gives lower yields and frequently causes decomposition of the diketones with the formation of resinous by-products.

[8] An enolisable product similar to (III) was prepared by Fischer and Cirulis.[9]

[6] D. Vorländer, C. Ihle, H. Volkholz, M. P. Neumann, G. von Brasche and W. Zeh, *Z. Anal. Chem.* **77**, 241 (1929).

[9] W. M. Fischer and A. Cirulis, *Liebigs Ann.* **514**, 261 (1934).

VOL. 6 1959

EXPERIMENTAL

Melting points are not corrected.

2-Methyl-3-acetylcinchoninic acid (Ia)

Acetylacetone (18 g, 6 moles) in ethanol (20 ml) was added to isatin (4·4 g, 1 mole) in aqueous potassium hydroxide (11·3 g, 15%, 1 mole), and the mixture heated for 6 hr. After evaporation of ethanol, the aqueous solution was extracted with ether and acidified with dilute HCl. The crude product (5 g, 72·7%), m.p. 189°, was crystallised from ethanol to give the pure acid (Ia) m.p. 198° (Found: C, 68·07; H, 4·98; N, 6·43. $C_{13}H_{11}O_3N$ requires: C, 68·11; H, 4·84; N, 6·11%).

(b) A mixture of dry potassium isatate* (2 g, 1 mole) and acetylacetone (5 g, 5 moles) was refluxed (3 hr) and on cooling, the solid product was washed twice with ether, dissolved in water (25 ml), and the solution acidified with dilute HCl. The precipitate was filtered (1·83 g, 79·9%) and crystallised from ethanol to give the pure acid, (Ia) m.p. 195–196°. It did not depress the melting point of a sample prepared according to (a).

Methyl 2-methyl-3-acetylcinchoninate. The acid (Ia, 4 g) was converted, in the usual manner, by means of diazomethane to the *methyl ester* m.p. 55–56° (from ethanol). (Found: C, 64·03; H, 5·74; N, 5·43; $C_{14}H_{15}O_3NH_2O$ requires: C, 64·35; H, 5·79; N, 5·36%). For analysis, the ester was dried under reduced pressure (20 mm) in the absence of drying agents. In the presence of phosphorus pentoxide or potassium hydroxide, the compound lost water of crystallisation and liquefied.

2-Methyl-3:4-quinoline dicarboxylic acid. A solution of sodium hypochlorite (344 g) (prepared by introducing 69 g of chlorine into 275 g of 20% aqueous sodium hydroxide, at 0°) was added to (Ia) (13 g, 1 mole) dissolved in 20% aqueous sodium hydroxide (11·4 g, 1 mole). After the vigorous reaction had subsided, the mixture was heated (steam-bath) for 30 min, chloroform was evaporated and the cooled solution treated with solid sodium hydrogen sulphite and the acid (13 g, 100%) precipitated with dilute HCl, and identified as the *dimethyl ester*, m.p. 61–62° (from petroleum ether), which was prepared according to Micović[4], *picrate*, m.p. 156°. Both compounds gave no depression of m.p. with the corresponding authentic samples.

3-Acetylquinaldine. The acid (Ia, 1·15 g) was slowly heated, under reduced pressure (15 mm), to 200°, when decarboxylation took place. On raising the temperature to 240°, an oil distilled which, on cooling, gradually solidified. After crystallisation from petroleum ether it melted at 74–75°[5] (Found: C, 77·82; H, 6·05; N, 7·70; Calc. for $C_{12}H_{11}ON$ C, 77·81; H, 5·99; N, 7·56%).

Quinaldine. The acid (Ia, 1 g) and powdered potassium hydroxide (2·5 g) and a few drops of water were heated with a free flame. The oil, which distilled with water, was dissolved in dilute HCl and converted into the yellow chloroplatinate of quinaldine, m.p. 226° (from water).

2-Methylcinchoninic acid

Freshly prepared acetylacetone (15 g, 3 moles) was dissolved in ethanol (30 ml) and added to isatin (7·3 g, 1 mole) in aqueous potassium hydroxide (56 g, 1 mole). After heating 8 hr (steam-bath), the mixture was treated as described above to give *2-methylcinchoninic acid* (6·8 g, 72·67%) m.p. 241° (from ethanol), did not depress the m.p. of an authentic sample, prepared from isatin and acetone.[10,11] (Found: C, 70·30; H, 4·87. Calc. for $C_{11}H_9O_2N$: C, 70·58; H, 4·85%).

2-Methyl-3-propionylcinchoninic acid (Ib)

A mixture of dry potassium isatate (2 g, 1 mole) and propionylacetone (6 g, 5·35 moles) was slowly heated to 150°. After the mixture had ceased reacting (about 20 min), the temp was maintained for 1 hr at 100° (prolonged heating at 150° gave resinous products). The cooled mixture was treated with water (50 ml) and the unreacted diketone extracted with ether. On acidifying the aqueous solution with dilute HCl the crude acid (Ib, 1·6 g, 66·7%) separated as an oil which solidified. It crystallised from aqueous ethanol m.p. 132° (Found: C, 68·9; H, 5·36; N, 5·82. $C_{14}H_{13}O_3N$ requires: C, 69·13; H, 5·38; N, 5·76%).

Quinaldine. This degradation product was obtained from (Ib) and identified.

* This salt was prepared from isatin and an equivalent amount of 20% aqueous potassium hydroxide, at temperatures below 40°. Using an excess of alkali, at higher temp, other products are formed (to be published).

[10] W. Pfitzinger, *J. Prakt. Chem.* **33**, 100 (1886).
[11] W. Pfitzinger, *J. Prakt. Chem.* **38**, 583 (1888); **56**, 283 (1897).

2-Methyl-3-benzoylcinchoninic acid (Ic)

A mixture of dry potassium isatate (4·1 g, 1 mole) and benzoylacetone (16 g, 4 moles) was heated at 120° (10 hr). On cooling, the product was treated with water (50 ml) and excess benzoylacetone removed with ether. The aqueous solution was acidified with dilute HCl and the filtered precipitate was extracted with 3% aqueous sodium hydrogen carbonate to separate the acid from unreacted isatin. Treatment of the bicarbonate solution with dilute HCl gave 2·4 g (41·8%) of (Ic). After crystallisation from ethanol-pyridine (8 : 2) it melted at 280° (Found: C, 74·30; H, 4·76; N, 4·66. $C_{18}H_{13}O_3N$ requires: C, 74·21; H, 4·49; N, 4·81%).

The condensation in water-ethanol solution in the presence of 1 mole of potassium hydroxide, as described above gave much lower yields of (Ic), namely, 7·5–26% for the crude product and depended upon the duration of heating (8–60 hr).

Methyl 2-methyl-3-benzoylcinchoninate. Treatment of the acid (Ic) with ethereal diazomethane, gave the corresponding *methyl ester* m.p. 119–120° (from ethanol) (Found: C, 74·97; H, 5·22; N, 4·47. $C_{19}H_{15}O_3N$ requires: C, 74·74; H, 4·95; N, 4·59%).

3-Benzoylquinaldine. The acid (Ic, 1·5 g) was slowly heated, under reduced pressure (5 mm), to 290–300°, when decarboxylation took place. On raising the temp to 310–320° *3-benzoylquinaldine* distilled which solidified on cooling. After crystallisation from ligroin, it melted at 61–62° [6] (Found: C, 82·50; H, 5·28; N, 5·79. Calc. for $C_{17}H_{13}ON$: C, 82·56; H, 5·30; N, 5·67%). *3-Benzoylquinaldine oxime*, m.p. 229–231° (from ethanol).[6]

Quinaldine. This was obtained from (Ic) and benzoic acid in the residue from the distillation was identified.

2-Phenylcinchoninic acid (*Cinchophen*)

To a solution of isatin (4·9 g,1 mole) in aqueous potassium hydroxide (37 g, 20%) benzoylacetone (5·35 g, 1 mole) in ethanol (30 ml) was added, and the mixture heated (steam-bath, 8 hr). Working up as described above gave cinchophen (5·5 g, 66·9%) m.p. 208–209° (from aqueous ethanol). The acid was identified by comparison with an authentic specimen prepared from isatin and acetophenone and by degradation to 2-phenylquinoline m.p. 83–84°, chloroplatinate m.p. 209°.

2-Phenyl-3-benzoylcinchoninic acid (Id)

A mixture of dry potassium isatate (4·1 g, 1 mole) and dibenzoylmethane (18 g, 4 moles) was heated (10 hr) at 140–150°. The condensation product was treated as described above to give crude (Id) (4·5 g, 63·2%). After several crystallisations from ethanol the m.p. was raised to 257° (Found: C, 77·98; H, 4·34; N, 4·01. $C_{23}H_{15}O_3N$ requires: C, 78·17; H, 4·28; N, 3·96%).

Methyl 2-phenyl-3-benzoylcinchoninate. This was prepared from (Id) and ethereal diazomethane and after crystallisation from ethanol melted at 159° (Found: C, 78·92; H, 4·67; N, 4·17. $C_{24}H_{17}O_3N$ requires: C, 78·46; H, 4·66; N, 3·81%).

2-Phenyl-3-benzoylquinoline. The acid (Id, 2 g) was slowly heated, under reduced pressure (5 mm), to a few degrees above its melting point (257–265°). After decarboxylation, the temp was raised to 290°. The base distilled and solidified on cooling, and on crystallisation from methanol, *2-phenyl-3-benzoylquinoline* melted at 133–135° [6] (Found: C, 85·25; H, 4·79; N, 4·54. $C_{22}H_{15}ON$ requires: C, 85·41; H, 4·89; N, 4·53%).

2-Phenylquinoline. This base was prepared from (Id) and potassium hydroxide as described for quinaldine. Recrystallised from dilute ethanol it melted at 83°.[12]

2-Methyl-3-acetonylcinchoninic acid (II)

A mixture of dry potassium isatate (2 g, 1 mole) and acetonylacetone (10·26 g, 9 moles) was heated for 2 hr at 160–180°. The unreacted diketone was removed by distillation under reduced pressure, and the residue was treated with water (100 ml). The insoluble resinous material was filtered and the filtrate acidified with dilute HCl and the precipitate (0·8 g, 32·9%) washed with ice-cold ethanol and crystallised from boiling water. *2-Methyl-3-acetonylcinchoninic acid* melted at 280–281° (Found: C, 69·70; H, 4·75; N, 5·62. $C_{14}H_{13}O_3N$ requires: C, 69·13; H, 5·38; N, 5·76%).

Attempts to condense isatin with acetonylacetone in aqueous potassium hydroxide failed. Only resinous material was obtained, which could not be purified.

[12] O. Doebner and W. von Miller, *Ber.* **16**, 1664 (1883).

2:3-*Dimethylquinoline*. (II, 0·5 g) and powdered potassium hydroxide (0·1 g) were treated as described for quinaldine. 2:3-*Dimethylquinoline* was crystallised from ether, m.p. 68°.[12] *Picrate*, m.p. 227–229° (from ethanol).[11]

Spiro[*octahydro*-1:8-*dioxoxanthene*-9:3′-*oxindole*] (IVa)

(a) A solution of isatin (0·74 g, 1 mole) and 1:3-*cyclo*hexanedione (1·12 g, 2 moles) in 75% aqueous ethanol (30 ml) was refluxed for 6 hr. Half of the ethanol was removed by distillation, and the crude product (1·3 g, 77·6%), which separated on cooling, was filtered and crystallised from ethanol, m.p. 339°,[8] and was insoluble in cold alkali. (Found: C, 71·46; H, 5·25; N, 4·19. Calc. for $C_{20}H_{17}O_4N$: C, 71·63; H, 5·11; N, 4·18%).

(b) The same quantities of reactants, but in the absence of solvent, were heated for 2 hr at 110–115°. On cooling, the mixture of solid products was triturated with cold ethanol (30 ml) and the undissolved material (1·5 g, 89·5%) was crystallised from ethanol, m.p. 339°. (Found: C, 71·39; H, 5·30; N, 3·94. Calc. for $C_{20}H_{17}O_4N$: C, 71·63; H, 5·11; N, 4·18%).

(c) A solution of isatin and *cyclo*hexanedione (same quantities as above) in glacial acetic acid (30 ml) was refluxed for 4 hr, cooled and poured into water (50 ml). The crude precipitate (0·65 g, 37·5%) was crystallised from ethanol, m.p. 339°.

Spiro[*octahydro*-3:6-*dimethyl*-1:8-*dioxoxanthene*-9:3′-*oxindole*] (IVb)

(a) Isatin (0·74 g, 1 mole) and 5-methyl-1:3-*cyclo*hexanedione (1·26 g, 2 moles) were treated as described above to yield (1 g, 55·1%) of crude (IVb) which crystallised from ethanol and melted at 300–301° and was insoluble in alkalies. (Found: C, 72·73; H, 5·82; N, 4·10. $C_{22}H_{21}O_4N$ requires: C, 72·72; H, 5·82; N, 3·86%).

(b) The same quantities of reactants, but in the absence of solvent, were heated for 2 hr at 130°. On cooling, the mixture was triturated with cold ethanol (30 ml) and the undissolved material (1·20 g, 66·1%) was crystallised from ethanol, m.p. 300°. (Found: C, 72·55; H, 5·71; N, 3·88. $C_{22}H_{21}O_4N$ requires: C, 72·72; H, 5·82; N, 3·86%).

(c) The same quantities of reactants were dissolved in glacial acetic acid (30 ml) and treated as described above. Crystallisation of the crude precipitate (1·2 g, 66·1%) from ethanol 300°.

1:2:3:4-*Tetrahydro*-3-*methyl*-1-*oxo*-9-*acridinecarboxylic acid* (Va)

A mixture of dry potassium isatate (8 g, 1 mole) and 5-methyl-1:3-*cyclo*hexanedione (5 g, 1 mole) was heated for 30 min at 130–140°. On cooling, the red solid was treated with water (50 ml), the insoluble portion was filtered and extracted with 6% aqueous sodium carbonate. The combined filtrates were acidified with HCl, the precipitate was filtered and triturated with ice-cold ethanol. Insoluble *tetrahydro*-3-*methyl*-1-*oxo*-9-*acridinecarboxylic acid* was filtered (1·5 g, 15·7%) and crystallised from a large volume of boiling ethanol, m.p. 258–259°. Equivalent 257·6 (calc. 255·26). (Found: C, 70·33; H, 5·20; N, 5·70. $C_{15}H_{13}O_3N$ requires: C, 70·58; H, 5·13; N, 5·49%).

The product, insoluble in water and sodium carbonate solution (1·7 g, 23·6%, based on the *cyclo*hexanedione), was crystallised from ethanol and gave *spiro*[*octahydro*-3:6-*dimethyl*-1:8-*dioxoxanthene*-9:3′-*oxindole*] (IVb), m.p. 300°. It did not depress the m.p. of an authentic sample prepared as described above. (Found: C, 72·53; H, 5·74; N, 4·17. $C_{22}H_{21}O_4N$ requires: C, 72·72; H, 5·82; N, 3·86%).

3:3-*Bis*[5′:5′-*dimethyl*-1′3′-*dioxo*-2′-*cyclohexyl*]*oxindole* (III)

(a) A solution of isatin (0·74 g, 1 mole) and methone (1·44 g, 1 mole) in ethanol (30 ml) was refluxed for 6 hr. A colourless product, m.p. 235–239°, crystallised upon cooling (1·3 g, 63·5%). Crystallisation from ethanol raised the m.p. to 249–250°. The compound was soluble in alkalies. (Found: C, 70·26; H, 6·62; N, 3·83. $C_{24}H_{29}O_5N$ requires: C, 70·39; H, 6·65; N, 3·42%).

(b) The same quantities of reactants, but in the absence of solvent, were heated for 2 hr at 140°. On cooling, the mixture was treated with cold ethanol (30 ml) and the undissolved material (1·4 g, 68·4%) was crystallised from ethanol, m.p. 249°. The m.p. was not depressed by admixture of a sample of (III) prepared above.

VOL. 6 1959

Spiro[octahydro-3:3:6:6-*tetramethyl*-1:8-*dioxoxanthene*-9:3′-*oxindole*] (IVc)

A solution of (IIIc, 1·36 g) glacial acetic acid (20 ml) was refluxed for 6 hr. On cooling, the solution was poured into water (45 ml) and the precipitate (1·2 g, 92·3%) was crystallised from ethanol. The compound melted at 294° (283–285°)* and did not depress the m.p. of a sample prepared (m.p. 294°) from methone and isatin, in glacial acetic acid. (Found: C, 73·60; H, 6·21; N, 3·68. Calc. for $C_{24}H_{25}O_4N$: C, 73·63; H, 6·43; N, 3·58%).

1:2:3:4-*Tetrahydro*-3:3-*dimethyl*-1-*oxo*-9-*acridinecarboxylic acid* (Vc)

A mixture of potassium isatate (20·3 g 1 mole) and methone (14·4 g, 1 mole) was heated for 30 min at 135–140°. On cooling, the red solid was treated with water (100 ml), the insoluble portion was filtered and extracted with cold 10% aqueous sodium hydroxide. The combined filtrates were acidified with HCl, the precipitate was filtered and triturated with ice-cold ethanol in order to eliminate the red solid. The remaining colourless *tetrahydroacridine carboxylic acid* was filtered (7 g, 26%) and crystallised from a large volume of boiling ethanol, m.p. 292°. Equivalent 265·4; calc. 269·29. (Found: C, 71·27; H, 5·58; N, 5·20. $C_{16}H_{13}O_3N$ requires: C, 71·36; H, 5·61; N, 5·20%).

The ethanolic extract was evaporated to dryness, the residue treated with 6% aqueous sodium carbonate and the insoluble part (3·8 g, 18·6%, based on methone) was filtered. After crystallisation from ethanol it melted at 249° and was soluble in alkalies. By mixed m.p. determination it was identified as (III).

The product insoluble in water and sodium hydroxide (7 g, 35·9%, based on methone) was crystallised from 50% aqueous ethanol to give (IVc), m.p. 294°. (Found: C, 73·76; H, 6·75; N, 3·50. $C_{24}H_{25}O_4N$ requires: C, 73·63; H, 6·43; N, 3·50%).

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VOL.
6
1959

THE STRUCTURE OF ψ-CONHYDRINE

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Abstract—The three-dimensional structure, except for the absolute configuration, of ψ-conhydrine has been determined in an X-ray diffraction study of ψ-conhydrine hydrobromide. In agreement with recent chemical evidence, the OH and propyl groups are found to be *trans* to each other, and in the equatorial position relative to the saturated six-membered ring. The unit cell is orthorhombic in the space group D_2^4-$P2_12_12_1$, contains four $C_8H_{18}NOBr$, and has dimensions $a = 15{\cdot}15$, $b = 9{\cdot}28$, $c = 7{\cdot}72$ A. Refinement, including anisotropic thermal motion, has yielded values of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0{\cdot}109$ and $r = \Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4 = 0{\cdot}056$ for the 920 observed reflections.

INTRODUCTION

CONHYDRINE and ψ-conhydrine were two of the members of the hemlock alkaloids whose configurations remained unknown at the time this study was originated. In the meantime, the stereochemistry of ψ-conhydrine has been established independently by Balenovic and Stimac,[1] and by Hill,[2] who disagree on the absolute configuration. Nevertheless, this study was completed in order to confirm the configuration of ψ-conhydrine by an independent method. A complete three-dimensional structure, except for absolute configuration, has now been obtained. In particular, the OH and propyl groups are found to be *trans* to each other. The very reasonable, but hitherto unproved, conclusion that OH and propyl groups are in the equatorial positions has also been reached in the present study. In addition, the exact three-dimensional geometry, molecular packing, and particularly the directions of hydrogen bonding, have been established; and it is hoped that these additional details may aid in the elucidation of the mechanisms of interactions of this type of molecule with other molecules in biosynthetic routes and in physiological activity.

EXPERIMENTAL

The synthesis of *dl*ψ-conhydrine,[3] the preparation of its HBr salt, and the establishment of its identity with the natural product were carried out by Leete. The crystals of ψ-conhydrine hydrobromide were needle-shaped and beautifully formed. A crystal 0·15 mm in diameter and 2 mm in length was chosen for the investigation.

The unit cell is orthorhombic, with parameters $a = 15{\cdot}15$, $b = 9{\cdot}28$ and $c = 7{\cdot}72$ A, where the c axis is parallel to the needle axis of the crystal. Systematic extinctions of $h00$ when h is odd, $0k0$ when k is odd and $00l$ when l is odd lead uniquely to the space group D_2^4-$P2_12_12_1$, which requires four or a multiple of four molecules in the unit cell. The assumption of four molecules leads to a reasonable calculated density of 1·37 g cm^{-3}. The space group also requires that in a single crystal all molecules have either the *d* form or the *l* form; therefore the separation of *d* and *l* form of the compound was completed in the process of crystallization.

Equi-inclination Weissenberg photographs were taken of levels 0, 1, 2, 3 and 4 about the c axis with Cu$K\alpha$ radiation, and precession photographs were taken, using Mo$K\alpha$ radiation, at $\mu = 30°$ of

[1] K. Balenovic and N. Stimac, *Crotica Chem. Acta* **29**, 153 (1957).
[2] R. K. Hill, *J. Amer. Chem. Soc.* **80**, 1611 (1958).
[3] L. Marion and W. F. Cockburn, *J. Amer. Chem. Soc.* **71**, 3402 (1949).

the $0kl$, $1kl$, $2kl$, $h0l$, $h1l$, hhl, $2kkl$ and $3kkl$ levels, at $\mu = 28°$ of the $3kl$ and $h2l$ levels and at $\mu = 25°$ of the $4kl$, $5kl$ and $h3l$ levels. A total of 920 independent diffraction maxima were estimated visually with the aid of two intensity scales, one for the Weissenberg photographs and another for the precession photographs, prepared from timed exposures of a "typical" reflection from the same crystal. Absorption and extinction errors were neglected. The usual Lorentz-polarization corrections were made and the reflections were correlated to a single scale with the use of reflections common to the several films. The absolute scale was later established by the use of statistical methods and refined by correlation with trial structures.

Structure determination

The three-dimensional Patterson function was computed with sharpened coefficients $\{F_o^2/(\hat{f})^2\} \exp[2(B - B')(\sin^2\theta/\lambda^2)]$, where $B - B'$ was chosen as $2A^2$ and $\hat{f} = \Sigma f_i/\Sigma Z_i$ in the usual notation. Due to the fact that the bromide ions occur in pairs nearly at $y = 0$ and $y = \frac{1}{2}$, the Patterson function possessed planes of symmetry at $y = 0$ and $y = \frac{1}{2}$. Therefore, there was a twofold ambiguity in the interpretation of the Patterson function.

Careful analysis of the shapes and the heights of the single and the pseudo double Br · · · Br peaks indicated that the Br's were displaced from $y = 0$ by $\pm 0{\cdot}28$ A and $y = \frac{1}{2}$ by $\mp 0{\cdot}28$ A. The choice of signs is arbitrary in the sense that the $-+$ combination and $+-$ combination correspond to different choices of origin in the space group when only Br are present. Another unusual feature of the Br · · · Br peaks was the elongation of the peaks along y, interpreted as pronounced anisotropic thermal motion of the Br ions, later verified as anisotropic motion of all atoms. Hence, the first three-dimensional electron density map was computed with the phases determined by the positions of Br ions only. The displacement of Br positions from $y = 0$ and $y = \frac{1}{2}$ was exaggerated a little to 0·3 A, in the hope that some improvement might be obtained in the separation of the true structure from its mirror image. All of the light atoms except hydrogen showed up in this map, along with some false peaks. The trial structure was selected on the basis of the known empirical formula of the compound, and the reasonableness of interatomic distances and the bond angles.

The first cycle of least-squares refinement with use of isotropic temperature factors yielded the very reassuring value of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ of 0·26, thus indicating the correct molecular geometry and Br positions. At this stage the O and C atoms had been introduced with their appropriate scattering factors. The identification of which peak of the six-membered ring was the N atom was left open at this stage by the use of the C scattering factors for all atoms in the six-membered ring. During the second cycle of least-squares refinement, the value of R fell only to 0·24, thus suggesting that anisotropic motions may be present. Four cycles of three-dimensional least-squares refinement were then made with anisotropic temperature factors of form $\exp -(\beta_1 h^2 + \beta_2 k^2 + \beta_3 l^2 + \beta_4 hk + \beta_5 kl + \beta_6 hl)$ for Br only, during which R fell to 0·18.

In the present study, we found a new use of the least-squares refinement. If one uses the C scattering factors for both N and C atoms in the least-squares refinement, the temperature factor of N decreases while that of C behaves normally. Thus, the temperature factor tends to adjust the total scattering factor of each atom. In this study, the temperature factor of C, which replaced N, had decreased from 3·0 A^2 to 2·8 A^2, while the temperature factors of other C atoms had increased to an average value of 4·5 A^2, thus indicating that use of a common scattering factor allows assignment of the correct identities of C, N, O atoms in a molecule by careful analysis of the behavior of temperature factors in the least-squares refinement.

At this stage, a three-dimensional difference electron density map was computed, in which the calculated map had a C atom in place of N. This map showed clearly the position of N, where the excess electron density was 1·3 eA^{-3}, and also showed strong anisotropic thermal motion of Br, as indicated by regions up to 3·1 eA^{-3} around Br. In addition, pronounced anisotropic thermal motion of the remainder of the molecule in the y direction was clearly indicated by peaks up to 0·8 eA^{-3} around nearly all atoms of the molecule. The remainder of the map showed no variation greater than 0·3 eA^{-3}. Thus, at this stage, expected peaks due to H atoms were overshadowed by the peaks due to anisotropic thermal motion of the molecule.

For subsequent cycles of least-squares refinement, the N scattering factor was introduced for N, all of the hydrogen atoms except those of the methyl group were placed at the positions calculated from the skeleton of the molecule, and all of the atoms except hydrogen were given anisotropic thermal parameters. The values of $\Sigma w(|F_o|^2 - |F_c|^2)^2$ for the next three cycles were 4188, 2749 and

2152, which indicated that further refinement of structure is still possible. Analysis of the shifts and the standard deviations of parameters indicated, however, that the further refinement would improve the thermal parameters but it would not improve the co-ordinates appreciably. Since the main purpose of the present study is to obtain the molecular geometry of this compound, the refinement of the structure was terminated at this point.

Final values of $R = 0{\cdot}109$ and $r = \Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4 = 0{\cdot}056$ were obtained. The final three-dimensional electron density map was computed, composite sections of which are shown in Fig. 1; the background is below 0·6 eA^{-3}. The agreement for different classes of reflection is shown in Table 1. A list of co-ordinates, anisotropic thermal parameters and corresponding isotropic equivalents for atoms in one molecule is given in Table 2. The observed amplitudes of scattering are listed in Table 3. The shape of the molecule, its packing and intermolecular distances in the crystal are shown in Fig. 2.

VOL. 6 1959

DISCUSSION

The standard deviations in co-ordinates, calculated from the residuals in the final least-squares refinement,[4] were essentially isotropic. The standard deviations in bond lengths estimated from the above result were 0·028, 0·023, 0·025, 0·012 A in the C · · · C, C · · · N, C · · · O, N · · · Br bond lengths, respectively. As an independent estimate, the mean distance of 1·518 A for the seven C · · · C bonds in the molecule gave a standard deviation of 0·028 A. Standard deviations in bond angles are about 3°. The final bond lengths and bond angles are given in Figs. 3 and 4, respectively.

The OH and propyl groups are trans to each other and in the equatorial position relative to the saturated six-membered ring (Fig. 2). The propyl groups are stretched out in the general directions of equatorial bonds (Figs. 1 and 2). The shortest N · · · Br contact, 3·27 A (Fig. 2), is shorter than the 1·95(Br^-) + 1·2(H) + 1·0(H — N) = 4·15 A non-interaction distance, and even shorter than the ordinary sum of Van der Waals radii, 1·95(Br^-) + 1·5(N^+) = 3·45 A, of N and Br. Thus there is very likely a fairly strong N^+—H · · · Br^- bond. Even the OH · · · Br^- seems to be hydrogen-bonded (Fig. 2). The sum of radii for O^- and Br^- is 1·35 + 1·95 = 3·50 A, but if H intervenes, then the non-interaction distance should be 0·95(OH) + 1·2(H) + 1·95(Br^-) = 4·10 A. Therefore, the observed distance of 3·31 A suggests an OH · · · Br^- hydrogen bond.

The method described by Rossmann and Lipscomb[5] to calculate directions and magnitudes of principal axes of the ellipsoid of vibration from thermal parameters was applied to those of Br ion. The three solutions of the cubic equation gave one real and two conjugate imaginary roots, when $\beta_1 \cdots \beta_6$ listed for Br in Table 2 were employed. But when the full shifts, which were less than 5 per cent for $\beta_1 \cdots \beta_3$ and as high as 30 per cent for $\beta_4 \cdots \beta_6$, of corresponding parameters indicated by the final least-squares refinement were applied to $\beta_1 \cdots \beta_6$, the three solutions became real. This result suggests that the anisotropy and interactions of the thermal parameters are as yet incompletely refined. Since the difference electron density map showed strong anisotropic thermal motion in the y direction, we decided to ignore the cross terms β_4, β_5 and β_6. Magnitudes of vibration in the x, y and z directions were then re-calculated for Br. The corresponding B's were then 3·35, 5·88, 2·65 A^2 in x, y and z directions, respectively, which seem very reasonable and suggest that this abbreviated interpretative procedure is satisfactory even when refinement of the thermal parameters is not complete.

[4] E. W. Hughes and W. N. Lipscomb, *J. Amer. Chem. Soc.* **68**, 1970 (1946).
[5] M. G. Rossmann and W. N. Lipscomb, *Tetrahedron* **4**, 263 (1958).

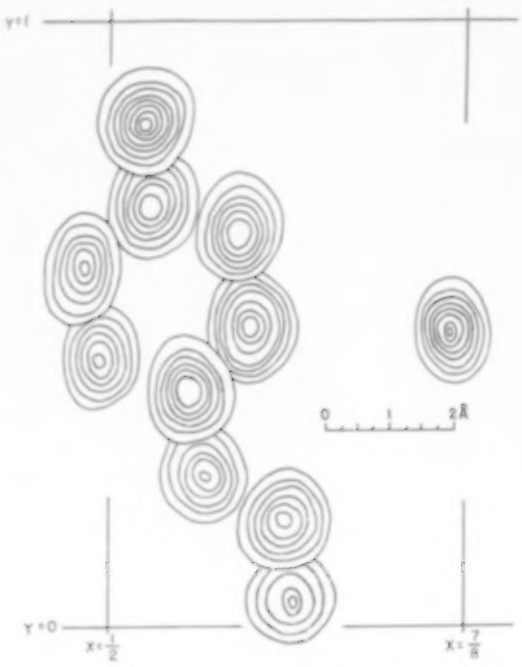

FIG. 1. Final electron density map. Contours are at intervals of 1 e/A³, except around bromine The lowest contour is at a height of 1 e/A³. Contours around bromine are at intervals of 4 e/A³ and the lowest contour is 4 e/A³.

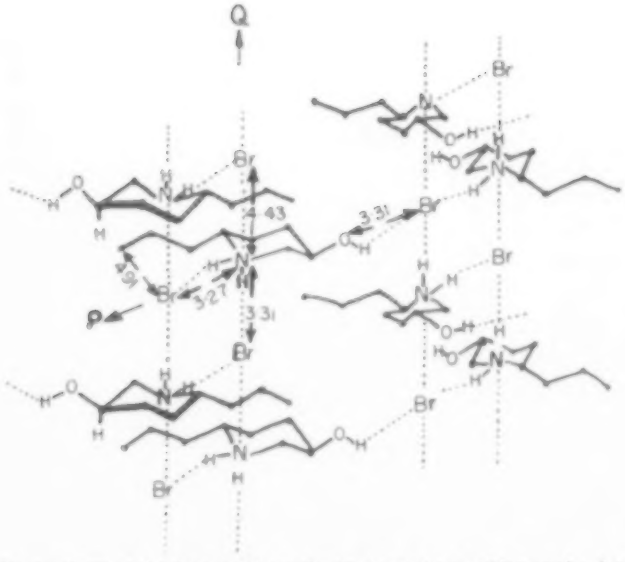

FIG. 2. Diagram showing the shape of the molecule, its packing and intermolecular distances.

VOL. 6 1959

TABLE 1. R FOR DIFFERENT CLASSES OF REFLECTIONS

Class	R	n	a	b
all	0·109	920	34	8
$0kl$	0·089	54	3	1
$h0l$	0·140	105	1	3
$hk0$	0·134	149	5	3
h odd	0·111	445	16	5
k odd	0·105	437	18	1
l odd	0·106	406	22	1
$h + k$ odd	0·107	472	12	6
$k + l$ odd	0·108	453	18	2
$h + l$ odd	0·110	455	20	6
$h + k + l$ odd	0·113	448	18	7

The number of reflections in each class is n. The number of planes showing $|F_o| > 2|F_c|$ is in column a, and those of $|F_o| < (\frac{1}{2})|F_c|$ are in column b.

TABLE 2. CO-ORDINATES AND THERMAL PARAMETERS OF ATOMS IN ONE MOLECULE

Atom	x/a	y/b	z/c	β_1	β_2	β_3	β_4	β_5	β_6	B in A²
C_1	0·584	0·389	0·518	0·0028	0·0164	0·0211	−0·0002	0·0009	0·0018	5·10
C_2	0·491	0·440	0·495	0·0041	0·0175	0·0280	0·0014	0·0010	0·0097	6·33
C_3	0·475	0·596	0·556	0·0037	0·0191	0·0210	0·0035	0·0028	0·0074	5·41
C_4	0·544	0·697	0·500	0·0041	0·0176	0·0173	0·0035	0·0022	−0·0036	4·69
C_5	0·637	0·643	0·543	0·0045	0·0159	0·0147	0·0037	−0·0044	0·0011	4·14
C_6	0·603	0·242	0·435	0·0050	0·0140	0·0241	0·0027	−0·0027	0·0011	5·39
C_7	0·686	0·170	0·488	0·0051	0·0191	0·0266	0·0032	−0·0019	−0·0077	6·33
C_8	0·710	0·038	0·372	0·0089	0·0209	0·0315	0·0078	−0·0021	−0·0044	7·43
N	0·651	0·494	0·463	0·0033	0·0144	0·0068	−0·0020	0·0039	0·0004	2·71
O	0·540	0·832	0·588	0·0090	0·0251	0·0442	0·0039	−0·0106	−0·0062	9·83
Br	0·864	0·484	0·536	0·0037	0·0170	0·0111	−0·0011	−0·0032	−0·0005	3·69

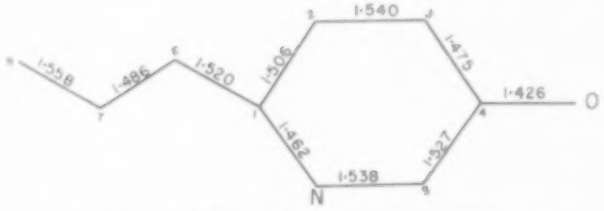

FIG. 3. Diagram showing bond length and atomic names.

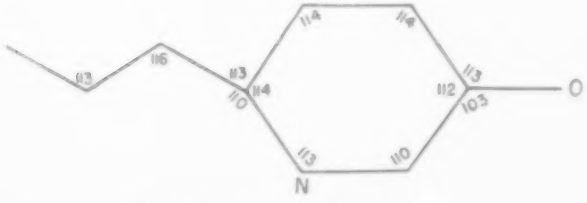

FIG. 4. Diagram showing bond angles.

The temperature factor of the oxygen atom behaved abnormally in the final anisotropic least-squares refinement (Table 2). However, since the isotropic temperature factor for this oxygen atom behaved normally in the earlier least-squares refinements, we feel that this later misbehavior is associated with compensation for unrefined anisotropic thermal parameters of the Br atom which is nearby. Since each cycle of three-dimensional least-squares refinement required one hour of computing time, we felt unwilling to carry out the necessary several refinements to test this surmise.

In Fig. 2, the directions P and Q are parallel to hydrogen bonding directions, which are also approximately parallel to x and z. Fairly "normal" amplitudes of vibration exist in the P, Q directions, while the amplitude of motion along y, perpendicular to PQ plane, is larger than these normal amplitudes. Even though the thermal parameters were not completely refined, the isotropic equivalents[6] of the thermal parameters for each atom were calculated. The resultant B's are listed in Table 2.

Had we been sure which molecular optical isomer was present in our particular small crystal, and had we been careful to photograph only one quandrant of reciprocal space, we no doubt could have established the absolute configuration from the type of data[7,8] which were obtained. However, modifications of our computing programs to include the effects of complex atomic scattering factors are still in progress, and hence the establishment of the absolute configuration from the X-ray evidence belongs to a later stage of this study.

Acknowledgments—We wish to thank Professor E. Leete who suggested this problem to us and who also supplied the sample of γ-conhydrine hydrobromide. It is a pleasure to acknowledge the support of this research by the Air Force Office of Scientific Research as well as a fellowship to H. S. Yanai by the Visking Co. For assistance in the use of the Remington Rand 1103 computer, we wish to thank Dr. M. G. Rossmann, Dr. R. A. Jacobson and Mr. F. S. Mathews. We also wish to thank the University of Minnesota for contribution of a portion of the 18 hr of computing time used in this study.

[6] M. G. Rossmann, R. A. Jacobson, F. L. Hirshfeld and W. N. Lipscomb, *Acta Cryst.* To be published.
[7] A. F. Peerdeman, *Acta Cryst.* **9**, 824 (1956).
[8] C. H. Dauben and D. H. Templeton, *Acta Cryst.* **8**, 841 (1955).

VOL.
6
1959

TABLE 3. OBSERVED STRUCTURE FACTORS*

00*l*, 2-8: 274.6, a, 86.7, a, 25.2, a, 13.2; 01*l*, 1-8: 12.7, 63.0, 7.7, 60.8, a, 49.2, a, 23.6; 02*l*, 0-4: 97.0, 13.0, 81.5, 17.1, 42.3; 03*l*, 1-6: 31.9, 36.7, 21.2, 33.4, 12.3, 26.0; 04*l*, 0-4: 62.3, a, 52.1, 3.8, 29.1; 05*l*, 1-4: 50.2, 6.2, 18.8, 18.7; 06*l*, 0-4: 43.3, 12.5, 40.9, 21.4, 22.6; 07*l*, 1-4: 17.0, 6.7, 11.3, 10.3; 08*l*, 0-4: 17.1, 7.0, 15.7, 11.6, 10.3; 09*l*, 1-4: 14.4, 4.3, 8.6, 5.3; 0,10,*l*, 0-4: 3.4, 3.3, 5.1, 4.6, 4.3; 0,11,*l*, 1-3: 3.8, a, 3.3; 10*l*, 2-8: 13.2, 22.4, 41.8, 32.4, 36.3, 29.8, 23.5; 11*l*, 0-4: 119.4, 21.9, 110.7, 16.6, 57.0; 12*l*, 0-7: 13.0, 20.9, 21.9, 36.5, 35.8, 31.5, 30.3, 23.8; 13*l*, 0-6: 77.1, 50.0, 73.5, 42.8, 37.5, 25.5, 14.5; 14*l*, 0-6: 7.4, 46.9, 4.6, 56.4, 19.9, 34.6, 19.7; 15*l*, 0-5: 35.3, 42.5, 35.1, 23.5, 23.8, 16.4; 16*l*, 0-4: 15.1, 12.3, 20.7, 14.9, 18.5; 17*l*, 0-4: 21.1, 17.8, 20.5, 16.4, 15.9; 18*l*, 0-4: 7.0, 9.1, 8.4, 9.1, 7.0; 19*l*, 0-4: 11.1, a, 11.1, 3.8, 9.1; 1,10,*l*, 0-3: 5.3, 5.6, 4.3, 5.0; 1,11,*l*, 3: 2.2; 20*l*, 0-5: 54.8, 9.2, 28.4, 40.9, a, 18.8; 21*l*, 0-7: 7.9, 50.7, 18.7, 65.6, 5.8, 60.6, a, 37.7; 22*l*, 0-5: 38.5, 127.6, 14.4, 75.0, 8.7, 21.4; 23*l*, 0-7: 22.8, 22.8, 18.2, 53.8, 4.3, 58.1, a, 39.4; 24*l*, 0-5: 29.6, 66.6, 21.2, 48.0, 19.2, 21.1; 25*l*, 0-5: 8.7, 15.9, 19.7, 30.0, 14.9, 26.4; 26*l*, 0-4: 12.1, 21.1, 14.2, 19.7, 17.3; 27*l*, 0-4: 24.0, 13.5, 21.7, 15.4, 9.2; 28*l*, 0-4: 5.2, 6.7, 10.4, 7.0, 14.0; 29*l*, 0-4: 7.9, a, 9.6, 3.8, 5.3; 2,10,*l*, 1-4: 3.8, 4.8, 3.3, 4.4; 2,11,*l*, 3: 2.2; 30*l*, 1-8: 60.0, 40.2, 89.5, 37.0, 61.0, 27.6, 34.9, 21.4; 31*l*, 0-6: 111.3, 127.3, 70.1, 63.5, 32.5, 20.7, 16.1; 32*l*, 0-7: 55.5, 45.7, 48.5, 51.4, 29.6, 48.1, 24.1, 35.6; 33*l*, 0-5: 44.5, 69.2, 29.0, 36.8, 12.3, 13.9; 34*l*, 0-7: 11.9, 28.6, 14.0, 39.4, 14.4, 31.0, a, 28.1; 35*l*, 0-5: 26.2, 33.1, 29.3, 31.3, 23.3, 15.9; 36*l*, 0-5: 19.2, 13.7, 21.7, 20.5, 17.5, 16.4; 37*l*, 0-4: 14.2, 9.8, 16.6, 11.1, 14.2; 38*l*, 0-4: 10.7, 10.2, 15.6, 8.7, 6.8; 39*l*, 0-4: 6.8, a, 9.2, 4.8, 5.3; 3,10,*l*, 0-3: 4.4, 3.9, 4.1, 4.4; 3,11,*l*, 3: 2.1; 40*l*, 0-4: 121.3, 25.5, 97.6, 20.0, 58.4; 41*l*, 0-8: 21.2, 29.8, 39.7, 13.2, 56.9, 19.5, 43.0, 14.0, 25.2; 42*l*, 0-4: 96.1, 12.5, 83.6, 13.2, 44.4; 43*l*, 0-7: 12.3, 13.5, 18.3, 27.7, 31.0, 22.8, 30.1, 16.4; 44*l*, 0-6: 67.0, 17.1, 56.9, 25.7, 26.9, 15.4, 16.8; 45*l*, 0-4: 10.3, 22.1, 19.4, 18.3, 23.3; 46*l*, 0-4: 39.2, 6.7, 33.7, 15.1, 22.8; 47*l*, 0-4: 13.4, 13.0, 12.8, 10.8, 13.7; 48*l*, 0-4: 28.6, 3.9, 20.7, 4.4, 10.8; 49*l*, 0-4: 3.9, 8.0, 4.1, 7.5, 3.4; 4,10,*l*, 2-4: 3.9, 3.9, 3.1; 4,11,*l*, 1-3: 4.1, a, 2.4; 50*l*, 1-8: 10.3, 34.4, 25.7, 50.0, 25.7, 42.7, 13.4, 23.3; 51*l*, 0-5: 159.5, 34.4, 105.9, 31.3, 44.2, 12.3; 52*l*, 0-6: 11.3, 15.6, 32.7, 10.3, 44.2, 20.0, 30.8; 53*l*, 0-5: 80.5, 53.8, 70.7, 35.5, 47.5, 13.5; 54*l*, 0-4: 13.9, 27.2, 26.0, 20.2, 32.2; 55*l*, 0-4: 42.7, 17.8, 37.8, 20.9, 24.0; 56*l*, 0-4: 15.1, 37.0, 16.1, 21.1, 17.1; 57*l*, 0-4: 28.1, 8.0, 26.4, 16.6, 15.7; 58*l*, 0-4: 7.5, 8.9, 8.4, 7.7, 7.5; 59*l*, 0-4: 5.0, a, 7.5, 3.6, 9.1; 5,10,*l*, 1-3: 5.6, 3.1, 2.9; 60*l*, 0-5: 85.1, 101.4, 52.6, 55.7, 25.7, 21.2; 61*l*, 0-7: 4.6, 27.2, 9.4, 39.4, 18.3, 39.1, 13.4, 30.0; 62*l*, 0-4: 69.5, 51.7, 55.7, 37.5, 30.1; 63*l*, 0-7: 46.4, 30.5, 27.2, 54.0, 14.7, 40.6, a, 21.2; 64*l*, 0-4: 28.8, 46.4, 28.4, 35.3, 22.1; 65*l*, 0-4: 20.4, 14.4, 14.7, 26.7, 8.6; 66*l*, 0-4: 22.3, 36.0, 23.1, 25.0, 15.7; 67*l*, 0-4: 14.7, 14.9, 13.2, 12.1, 7.7; 68*l*, 2-4: 10.4, 6.7, 11.3; 69*l*, 0-4: 10.3, a, 7.9, 4.6, 5.3; 6,10,*l*, 1-3: 3.8, 3.3, 2.7; 70*l*, 1-7: 15.4, 7.0, 47.1, 18.8, 51.9, 20.7, 41.5; 71*l*, 0-5: 55.0, 51.4, 31.2, 47.6, 17.5, 18.0; 72*l*, 0-7: 23.0, 22.1, 27.2, 50.0, 25.0, 51.2, a, 31.3; 73*l*, 1-5: 47.6, 15.9, 38.2, 23.0, 14.4; 74*l*, 0-4: 16.4, 14.5, 15.7, 32.2, 8.4;

* Unobserved reflections are represented by "a"

TABLE 3.—*continued*

75*l*, 1–4: 30.5, 7.4, 24.5, 13.5; 76*l*, 1–4: 14.0, 5.1, 19.4, 5.8; 77*l*, 0–4: 8.6, 13.5, 7.5, 14.5, 8.7; 78*l*, 0–4: 10.4, 6.5, 9.1, 6.8, 4.8; 79*l*, 1–4: 7.4, 3.6, 6.3, 6.0; 7,10,*l*, 0–2: 5.6, a, 5.5; 80*l*, 0–4: 84.1, 44.9, 59.4, 25.2, 33.9; 81*l* 0–8: 44.4, 22.1, 32.9, 36.8, 38.2, 25.9, 27.4, 20.2, 17.8; 82*l*, 0–4: 81.5, 42.3, 63.0, 23.8, 34.9; 83*l*, 0–6: 4.1, 10.8, 12.8, 19.0, 24.7, 23.3, 25.3; 84*l*, 0–5: 46.1, 20.4, 38.8, 17.1, 24.8, 13.5; 85*l*, 0–4: 5.6, 31.0, 10.4, 25.9, 17.6; 86*l*, 0–4: 14.9, 6.5, 15.9, 15.1, 13.7; 87*l*, 0–4: 8.2, 15.4, 8.4, 12.3, 9.8; 88*l*, 0–4: 11.3, 7.0, 9.2, 6.5, 7.5; 89*l*, 0–3: 5.0, 6.3, 4.3, 4.8; 8,10,*l*, 2–3: 3.3, 2.6; 90*l*, 1–6: 7.7, 35.6, 15.4, 45.6, a, 32.5; 91*l*, 0–4: 76.6, 9.2, 58.9, 6.7, 33.7; 92*l*, 0–4: 5.8, 8.7, 18.8, a, 26.5; 93*l*, 0–5: 59.8, 13.9, 45.1, 15.4, 21.4, 15.2; 94*l*, 0–4: 7.0, 15.1, 18.2, 12.5, 24.5; 95*l*, 0–4: 45.1, 17.3, 40.2, 20.7, 26.0; 96*l*, 1–4: 20.4, 13.2, 11.1, 15.4; 97*l*, 0–4: 22.4, a, 17.6, 7.5, 11.1; 98*l*, 0–4: 4.8, 9.8, 4.1, 6.3, 4.4; 99*l*, 0–3: 5.0, 3.9, 4.3, 4.4; 9,10,*l*, 0–1: 2.4, 2.6; 10,0,*l*, 0–5: 55.7, 54.1, 43.2, 42.0, 23.3, 22.6; 10,1,*l*, 0–7: 21.1, 23.5, 17.8, 29.8, 22.3, 26.7, 14.0, 14.4; 10,2,*l*, 0–4: 43.3, 48.5, 30.0, 28.3, 19.0; 10,3,*l*, 0–5: 17.0, 8.0, 20.0, 18.2, 20.4, 22.1; 10,4,*l*, 0–4: 27.1, 25.3, 26.0, 20.5, 18.2; 10,5,*l*, 0–4: 5.6, 9.2, 8.2, 11.8, 9.2; 10,6,*l*, 0–4: 25.9, 10.4, 19.7, 10.4, 11.5; 10,7,*l*, 0–4: 14.9, a, 11.1, 4.4, 5.5; 10,8,*l*, 0–4: 6.8, 6.3, 7.5, 4.8, 8.4; 10,9,*l*, 0–2: 5.6, a, 5.5; 10,10,*l*, 0: 3.3; 11,0,*l*, 1–7: 11.6, 5.1, 26.9, 3.9, 28.3, a, 25.0; 11,1,*l*, 0–5: 22.6, 51.6, 12.8, 34.9, 8.0, 13.5; 11,2,*l*, 0–5: 21.4, 14.7, 16.4, 33.1, 11.9, 32.7; 11,3,*l*, 1–5: 43.0, 11.1, 36.0, 14.0, 19.5; 11,4,*l*, 0–4: 21.7, 10.1, 15.9, 21.1, 6.8; 11,5,*l*, 1–4: 16.8, 4.6, 13.7, 5.8; 11,6,*l*, 0–4: 15.2, 4.4, 11.6, 8.6, 7.0; 11,7,*l*, 1–4: 9.4, 6.8, 7.5, 8.4; 11,8,*l*, 0–3: 6.2, a, 5.3, 4.4; 11,9,*l*, 1–2: 2.6, 3.6; 12,0,*l*, 0–4: 39.9, 28.4, 29.8, 21.4, 14.0; 12,1,*l*, 0–6: 15.6, 12.8, 18.8, 21.9, 20.2, 24.0, 14.4; 12,2,*l*, 0–4: 22.4, 18.5, 19.5, 17.5, 14.7; 12,3,*l*, 0–5: 7.5, 10.1, 15.2, 21.4, 17.3, 25.9; 12,4,*l*, 0.4: 21.6, 21.7, 17.3, 15.6, 13.7; 12,5,*l*, 0–4: 4.3, 14.2, 6.7, 15.1, 9.6; 12,6,*l*, 0–4: 14.7, 11.6, 11.9, 11.3, 7.9; 12,7,*l*, 1–4: 8.0, 3.3, 7.9, 3.9; 12,8,*l*, 0–3: 5.6, 4.3, a, 5.0; 12,9,*l*, 1: 3.9; 13,0,*l*, 1–6: 3.3, 22.1, 6.7, 31.0, a, 23.5; 13,1,*l*, 0–4: 48.0, 5.6, 30.7, 4.3, 22.1; 13,2,*l*, 0–4: 7.9, 4.4, 14.7, 7.0, 20.2; 13,3,*l*, 0–4: 33.9, 4.6, 25.9, a, 17.1; 13,4,*l*, 0–4: 5.0, 12.1, 8.2, 9.4, 13.0; 13,5,*l*, 0–4: 20.9, 3.3, 17.1, 9.6, 11.6; 13,6,*l*, 0–4: 4.8, 11.9, 5.0, 8.9, 7.5; 13,7,*l*, 0–4: 8.2, 3.3, 6.3, 5.0, 4.6; 13,8,*l*, 1–3: 7.4, 3.3, 5.0; 14,0,*l*, 0–4: 38.9, 14.5, 29.0, 12.8, 15.9; 14,1,*l*, 0–4: 11.8, 4.3, 13.7, 8.9, 16.6; 14,2,*l*, 0–4: 43.2, 17.5, 27.9, 14.4, 16.3; 14,3,*l*, 0–4: 9.8, 10.9, 9.1, 8.2, 9.7; 14,4,*l*, 0–4: 20.2, 13.9, 16.4, 10.4, 11.9; 14,5,*l*, 0–4: 4.6, 8.0, 7.7, 7.2, 6.7; 14,6,*l*, 0–4: 11.9, 5.5, 9.4, 6.3, 5.8; 14,7,*l*, 1–3: 6.5, 3.3, 2.6; 14,8,*l*, 0–1: 6.5, 3.8; 15,0,*l*, 1–4: 6.8, 3.8, 17.6, 4.3; 15,1,*l*, 0–4: 12.1, 24.0, 9.2, 16.8, 6.0; 15,2,*l*, 0–4: 7.0, 6.7, 4.1, 15.1, 3.6; 15,3,*l*, 0–4: 5.3, 20.7, 7.4, 13.5, 7.7; 15,4,*l*, 0–4: 5.1, 4.1, 6.0, 7.9, 3.3; 15,5,*l*, 0–4: 5.8, 11.8, 4.1, 10.4, 2.7; 15,6,*l*, 0–3: 5.1, a, 5.1, 5.1; 15,7,*l*, 0–2: 7.5, 4.3, 5.6; 16,0,*l*, 0–4: 6.8, 25.3, 7.0, 18.5, 6.0; 16,1,*l*, 1–4: 5.1, 4.3, 11.3, 5.5; 16,2,*l*, 0–4: 8.2, 14.4, 7.0, 11.8, 5.8; 16,3,*l*, 0–4: 4.3, 6.7, 5.0, 11.9, 6.0; 16,4,*l*, 0–4: 4.3, 12.3, 3.9, 11.5, 3.8; 16,5,*l*, 0–3: 77.7, 3.9, 5.8, 7.0; 16,6,*l*, 0–1: 3.3, 4.3; 17,0,*l*, 1–4: 2.7, 8.2, 3.9, 11.8; 17,1,*l*, 1–4: 18.7, 3.1, 11.8, 3.6, 7.4; 17,2,*l*, 1–4: 3.25, 5.8, 4.6, 8.0; 17,3,*l*, 0–4: 12.7, 5.8, 9.9, 4.8, 6.0; 17,4,*l*, 1–3: 4.8, 5.3, 5.1; 17,5,*l*, 0–2: 7.5, 4.4, 4.4; 18,0,*l*, 0–3: 27.7, 9.4, 23.8, 5.5; 18,1,*l*, 2: 6.7; 18,2,*l*, 0–3: 15.6, 4.6, 10.3, 3.8; 18,3,*l*, 0–2: 3.8, 2.2, 4.3; 18,4,*l*, 0–1: 7.4, 3.9; 19,0,*l*, 2: 2.1; 19,1,*l*, 0–2: 10.4, 7.5, 5.8; 19,2,*l*, 0: 3.4.

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VOL. 6 1959

THE "POSITIVE HALOGEN" REACTION BETWEEN BENZOTRICHLORIDES AND POTASSIUM IODIDE

RELEVANT MECHANISTIC AND STERIC ASPECTS*

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Abstract—The "positive halogen" reactions of 2:3:4:5-tetrachlorobenzotrichloride and perchlorotoluene with potassium iodide in aqueous acetic acid, at 100°, have been investigated. In the case of the perchlorotoluene the products are the two isomeric *perchlorostilbenes* along with some 2:3:4:5:6-pentachlorobenzylidene chloride. The chief product of the reaction of 2:3:4:5-tetrachlorobenzotrichloride with potassium iodide is α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-*dodecachlorobibenzyl*; considerable amounts of the two isomeric α:2:3:4:5:α′:2′:3′:4′:5′-*decachlorostilbenes* have been isolated. Under the same conditions the α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl reacts with potassium iodide to give the corresponding decachlorostilbenes.

When the reaction of perchlorotoluene with potassium iodide is performed in aqueous acetic acid containing toluene the yield of 2:3:4:5:6-pentachlorobenzylidene chloride is greatly increased and benzyl iodide is formed.

The mechanisms of these reactions are discussed. It is shown that the results are consistent with the occurrence of the reaction through the intermediate α:α-dichlorobenzyl radicals and α:α:α′:α′-tetrachlorobibenzyls, the latter being formed by dimerization of the former.

The ultra-violet absorption spectra of the geometric isomers of α:α′-dichlorostibene, α:2:3:4:5:-α′:2′:3′:4′:5′-decachlorostilbene and perchlorostilbene are recorded and interpreted. It is shown that the higher-melting isomerides have the *trans* configuration and that, as a result of the strong steric interaction between the *alpha* chloride atoms and the *ortho* atoms, there exists strong inhibition to resonance in the *trans* forms.

INTRODUCTION

THE reaction of an organic halide with an inorganic iodide leads usually to substitution of the halogen by iodine. However, with organic halides the halogen of which is bonded to a carbon atom bearing electron-attracting groups, such as carbonyl, carboalkoxyl, nitro, etc, it may result instead in the oxidation of the iodide ion to iodine.[1–7] Such organic halides are said to show "positive halogen" reactivity. This has been attributed to a decreased polar character of the carbon-halogen bond due to the polarization induced by the electron-attracting groups which tends to reverse the normal polarization of the bond.[8] Iodides are not the sole reactants towards which "positive halogen" reactivity is displayed.[9]

From the viewpoint of the nature of the reaction products the "positive halogen" reactions with iodide ion can be grouped into three classes:

* The present article contains material presented in the XIV and XVI International Congresses of Pure and Applied Chemistry, held in Zurich (1955) and Paris (1957), respectively.

[1] J. V. Backes, R. W. West and M. A. Whiteley, *J. Chem. Soc.* **119**, 359 (1921).
[2] H. Finkelstein, *Ber.* **43**, 1528 (1910).
[3] H. Finkelstein, *Ber.* **43**, 1535 (1910).
[4] M. Weizmann and J. Edlitz, *Bull. Soc. Chim. Fr.* **53**, 1495 (1933).
[5] R. Willstätter and V. Hottenroth, *Ber.* **37**, 1775 (1904).
[6] A. Perret and R. Perrot, *Bull. Soc. Chim. Fr.* **1**, 1547 (1934).
[7] J. E. Leffler, *J. Amer. Chem. Soc.* **75**, 3598 (1953); M. F. Hawthorne, *Ibid.* **77**, 5739 (1955).
[8] W. A. Waters, *The Chemistry of Free Radicals* p. 252. Clarendon Press, Oxford (1946); E. D. Hughes, *Quart. Rev.* **5**, 253, 266 (1951).
[9] R. Altschul and P. D. Bartlett, *J. Org. Chem.* **5**, 623 (1940).

Class 1. Reactions leading to replacement of the "positive halogen" by hydrogen, e.g.: the reaction of phenacyl bromide which gives acetophenone,[1] and the reaction of alkyl bromonitromalonates, which gives alkyl nitromalonates.[5]

Class 2. Reactions yielding condensation products by union of the two groupings bonded to the "positive halogen", e.g.: the reaction of alkyl bromomalonates, which gives alkyl ethanetetracarboxylates.[2,4] When there is more than one "positive halogen" bonded to the same carbon atom the condensation product may undergo vicinal dehalogenation by iodide ion yielding an ethylene. Such is the case of the reaction of alkyl dibromomalonates which gives alkyl ethylenetetracarboxylates,[2,4] and the reaction of dichlorodiphenylmethane, which gives tetraphenylethylene, although the intermediate symmetrical dichlorotetraphenylethane can be isolated as well.[3]

Class 3. Reactions yielding the grouping bonded to the "positive halogen" as a relatively stable free radical, e.g.: the reaction of the triphenylmethyl chloride[6] and the reaction of tris(*p*-nitrophenyl)methyl bromide[7] yielding the corresponding free triarylmethyl radicals.

Each chlorine atom of a trichloromethyl group is subjected at least to the electron-attracting activity of the other two chlorine atoms. It is therefore reasonable to assume that at least one of them may show "positive halogen" reactivity. Accordingly, it is found that trichloromethyl derivatives such as benzotrichloride, 2:3:4:5-tetrachlorobenzotrichloride, 2:3:5:6-tetrachlorobenzotrichloride, perchlorotoluene and trichloroacetic acid react easily with sodium or potassium iodide, in acetic acid solution, with liberation of iodine. Chloroform, carbon tetrachloride and hexachloroethane fail however to react with iodide ion under the same conditions. Nesmeyanov *et al.* have found 1:1:1-trichloroalkanes, such as 1:1:1-trichloropentane, are inert at the trichloromethyl group towards sodium iodide.[10] Apparently, the trichloromethyl group does not display an oxidising character towards iodide ion when bonded to a saturated carbon atom.

As it might be expected, dichloromethyl derivates, such as benzylidene chloride* and pentachlorobenzylidene chloride fail to liberate iodine. However, it has been pointed out[2,3] that dichlorodiphenylmethane reacts with iodide ion. Therefore, a phenyl group can replace a chlorine atom, in this case, without loss of the "positive halogen" reactivity.

The present work has been devised in order to ascertain the nature of the products of the "positive halogen" reaction of benzotrichlorides with potassium iodide, and to obtain information regarding the reaction mechanism. Only the reactions of 2:3:4:5-tetrachlorobenzotrichloride and perchlorotoluene with potassium iodide in acetic acid are to be considered here in detail.

RESULTS

The reaction of perchlorotoluene with potassium iodide in aqueous acetic acid, after 22·5 hr at 100°, gave a mixture of *cis*-perchlorostilbene, m.p. 230·5–231·5°, *trans*-perchlorostilbene, m.p. ca. 400°, and some 2:3:4:5:6-pentachlorobenzylidene chloride. The yields were 47·5 per cent for the *cis* isomer and 36·6 per cent for the *trans* isomer. The pentachlorobenzylidene chloride formed, accounted only for

* See also reference 6.

[10] A. N. Nesmeyanov, R. K. Freidlina and L. I. Zakharkin, *Dokl. Akad. Nauk SSSR* **96**, 87 (1954); *Quart. Rev.* 330 (1956).

8·9 per cent the initial perchlorotoluene. When the reaction was stopped before completion (2·5 hr) no intermediate was isolated. The reaction takes place very slowly at room temperature. Under the same reaction conditions, but in the absence of potassium iodide, some hydrolysis of perchlorotoluene occurs. When the acetic acid used was not chromic acid-purified the yield of pentachlorobenzylidene chloride increased and, accordingly, the combined yields of perchlorostilbenes diminished.

The reaction took place by substituting iodine for potassium iodide After 22·5 hr at 100° the yields were 21 per cent for the *cis*-perchlorostilbene, 15 per cent for the *trans*-perchlorostilbene, and 40 per cent for the pentachlorobenzylidene chloride.

Ferrous chloride could also be substituted for potassium iodide.

The perchlorostilbenes were obtained by the reaction of perchlorotoluene with powdered copper and pyridine, according to Karrer's method of condensation of organic halides.[11]

The molecular magnitude of the perchlorostilbenes was determined by Rast's method, with camphor.

The structure of the *trans* isomer was ascertained by nuclear perchlorination of *trans*-α:α-dichlorostilbene with Silberrad's chlorinating agent[12] which gave a good yield of the product.

The isomerisation of *cis*-perchlorostilbene into the *trans* form was performed in dioxane solution by ultra-violet light. The yield was 62 per cent. No isomerisation took place, starting from either isomer, using iodine as a catalyst and working under the condensation conditions.

Attempts to convert the perchlorostilbenes into a common derivative failed. Dechlorination (with powdered zinc) of the *trans* isomer yielded a product giving the chlorine analysis of perchlorotolane, while the *cis* isomer gave a product with a smaller chlorine content. They were not investigated further.

Attempted degradations of the perchlorostilbenes with chromic acid (hot acetic acid solution) or warm fuming nitric acid in the presence of mercuric ions failed, for the perchlorostilbenes are quite stable towards such oxidising agents.

When the reaction of perchlorotoluene with potassium iodide was carried out, under nitrogen, in acetic acid containing 20 per cent of purified toluene, pentachlorobenzylidene chloride accounted for about half the starting perchlorotoluene. Benzyl iodide was also isolated. The yields referred to the initial perchlorotoluene were: pentachlorobenzylidene chloride, 47·5 per cent; *cis*-perchlorostilbene, 23·1 per cent; *trans*-perchlorostilbene, 19·1 per cent. Assuming that from every molecule of pentachlorobenzylidene chloride formed a molecule of toluene is converted into benzyl iodide, the amount of the latter was 55·3 per cent of the theoretical. The presence of toluene left the ratio of the yields of perchlorostilbenes practically unchanged.

It was found that under the reaction conditions, neither benzyl iodide resulted from attack of the liberated iodine on toluene nor pentachlorobenzylidene chloride by a direct reaction between toluene and perchlorotoluene.

[11] P. Karrer, W. Wehrli, E. Biedermann and M. dalla Vedova, *Chem. Zentr.* **I**, 1394 (1928); L. V. Johnson, F. Smith, M. Stacey and J. C. Tatlow, *J. Chem. Soc.* 4710 (1952).
[12] O. Silberrad, *J. Chem. Soc.* **119**, 2029 (1921); *Ibid.* **121**, 1015 (1922).

VOL. 6 1959

The reaction of 2:3:4:5-tetrachlorobenzotrichloride with potassium iodide was less rapid than that of perchlorotoluene under the same conditions. The former, after 5 days at 100°, yielded chiefly α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl, m.p. 252–253°, with *cis*-α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbene, m.p. 141–142° and *trans*-α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbene, m.p. 255–257°.

The reaction was also performed using ferrous chloride instead of potassium iodide.

It was found that α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl reacts with potassium iodide to give a mixture of *cis*- and *trans*-decachlorostilbenes.

The isomerisation of *cis*-decachlorostilbene into its *trans* form was effected in carbon tetrachloride solution by ultra-violet light. The yield was 66·2 per cent.

Attempts to obtain perchlorobibenzyl by nuclear chlorination of α:α:2:4:3:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl with Silberrad's chlorinating agent failed. The result was a mixture containing mostly *trans*-perchlorostilbene (83·8 per cent yield) with some of its *cis* isomer (3·2 per cent yield).

The dodecachlorobibenzyl is stable towards hot concentrated sulphuric acid or boiling acetic acid.

DISCUSSION

Mechanisms

The α:α:α′:α′-tetrachlorobibenzyls as intermediates. The reaction of perchlorotoluene with iodide ion occurs mostly according to the following stoicheiometry:

$$2C_6Cl_5CCl_3 + 4I^{\ominus} = C_6Cl_5CCl{=}CClC_6Cl_5 + 2I_2 + 4Cl^{\ominus}$$

It belongs therefore to the previously considered class 2, although class 1 reaction is also taking place.

The reaction might proceed either through perchlorobibenzyl as an intermediate, as in the case of the reaction of benzophenone chloride,[3] or by 1:1-elimination of a molecule of chlorine at the trichloromethyl group giving perchlorobenzylidene radical which would dimerise

Kinetics[13a] as well as structural[13b] evidence has been reported recently for such type of bivalent (carbene) radicals in certain reactions, such as the hydrolysis of chloroform.

In the case of the reaction of 2:3:4:5-tetrachlorobenzotrichloride, the isolation of dodecachlorobibenzyl along the decachlorostilbenes, and the liability of the former to undergo dechlorination with iodide ion under the same condensation conditions shows that the dodecachlorobibenzyl is indeed an intermediate of the reaction. This is circumstantial evidence for the presence of perchlorobibenzyl in the reaction of perchlorotoluene.

The results obtained when the reaction is carried out in the presence of *cyclo*hexene do not support the bivalent radical mechanism.[14]

[13a] J. Hine, *J. Amer. Chem. Soc.* **72**, 2438 (1950); [b] W. von E. Doering and A. K. Hoffmann, *Ibid.* **76**, 6162 (1954).

[14] M. Ballester and J. Rosa, unreported experiments.

VOL. 6 1959

Assuming that dechlorination of perchlorobibenzyl proceeds more rapidly than its formation from perchlorotoluene its concentration can never reach a substantial value. This is in full agreement with the failure to isolate perchlorobibenzyl when the reaction was stopped before completion.

Steric assistance due to compression between the *ortho* chlorine atoms and those of the *alpha* carbons might be the reason for the extreme readiness with which the perchlorobibenzyl undergoes dechlorination. Such internal steric strain is probably the reason also for the failure to obtain perchlorobibenzyl by nuclear chlorination of dodecachlorobibenzyl.

The α:α-dichlorobenzyls as intermediates. The condensations of benzotrichlorides yielding tetrachlorobibenzyls and/or dichlorostilbenes have also been carried out by means of metals or reducing inorganic ions.[15] The reactions of 2:3:4:5-tetrachlorobenzotrichloride and perchlorotoluene with ferrous chloride described are the best examples that can be given. These reducing agents are known to yield free radicals when reacting with organic halides. Also, the decomposition of benzoyl peroxides in benzotrichlorides give α:α:α′:α′-tetrachlorobibenzyls, presumably by dimerisation of α:α-dichlorobenzyl radicals.[16] On the other hand, the existence of reactions of class 3 shows that, when the grouping bonded to the "positive halogen" is stable enough, iodide ion can give it as a free radical.

There is, therefore, good evidence supporting a mechanism involving perchlorobenzyl radical as a reactive intermediate in the reaction of perchlorotoluene with potassium iodide.

The results of the reaction of perchlorotoluene with iodide ion are therefore consistent with the following sequences.

$$C_6Cl_5CCl_3 + 2I^{\ominus} \longrightarrow C_6Cl_5\dot{C}Cl_2 + I_2 + Cl^{\ominus}$$

$$2C_6Cl_5\dot{C}Cl_2 \longrightarrow C_6Cl_5CCl_2CCl_2C_6Cl_5$$

$$C_6Cl_5CCl_2CCl_2C_6Cl_5 + 2I^{\ominus} \longrightarrow C_6Cl_5CCl{=}CClC_6Cl_5 + I_2$$

cis and *trans*

It is well known that alkylaromatic hydrocarbons having hydrogen bonded to *alpha* carbon atoms can act as hydrogen donors in free radical reactions.[17] This is due to benzyl radical–resonance stabilisation.[18] That fact might be the explanation for the formation of pentachlorobenzylidene chloride in the pyrolysis of perchlorotoluene. In this pyrolysis perchlorobenzyl radical is, presumably, formed by carbon–chlorine bond fission.[19]

Therefore, the results of reaction of perchlorotoluene with potassium iodide in the presence of toluene should be regarded as a hydrogen-atom transfer reaction between toluene and perchlorobenzyl radical, which reaction competes with the dimerisation of the latter. The benzyl radical formed would then react with iodine to give benzyl iodide.

$$C_6Cl_5\dot{C}Cl_2 + C_6H_5CH_3 \longrightarrow C_6Cl_5CHCl_2 + C_6H_5\dot{C}H_2$$

$$C_6H_5\dot{C}H_2 + I_2 \longrightarrow C_6Cl_5CH_2I + I$$

[15] A. Onufrowicz, *Ber.* **17**, 833 (1884); F. Fox, *Ibid.* **26**, 653 (1893); J. Kenner and E. Witham, *J. Chem. Soc.* **97**, 1962 (1910); Y. Ogata and R. Oda, *Chem. Abstr.* **43**, 2194 *d* (1949).
[16] R. L. Dannley and M. Sternfeld, *J. Amer. Chem. Soc.* **76**, 4543 (1954).
[17] M. S. Kharasch, H. C. McBay and W. H. Urry, *J. Org. Chem.* **10**, 401 (1945); J. H. Raley, F. F. Rust and W. E. Waughan, *J. Amer. Chem. Soc.* **70**, 1336 (1948); E. C. Kooyman and A. Strang, *Rec. Trav. Chim.* **72**, 329 (1953); C. S. Rondestvedt and H. S. Blanchard, *J. Amer. Chem. Soc.* **77**, 1769 (1955).
[18] M. Szwarc, *Chem. Rev.* **47**, 75 (1950).
[19] M. Ballester and C. Molinet, *An. Real Soc. Españ. Fis. y Quim.* **54 B**, 151 (1958).

The fact that the molar ratio benzyl iodide pentachlorobenzylidene chloride is only about half the expected value is probably due to solvolysis of benzyl iodide and also by some reaction of benzyl radical with impurities of oxygen.[20]

It has been reported that alkylaromatic hydrocarbons can give hydride-ion transfers to carbonium ions.[21]

Therefore, a carbonium ion mechanism might account for the formation of pentachlorobenzylidene chloride.

$$C_6Cl_5CCl_3 \longrightarrow C_6Cl_5\overset{\oplus}{C}Cl_2 + Cl^{\ominus}$$

$$C_6Cl_5\overset{\oplus}{C}Cl_2 + C_6H_5CH_3 \longrightarrow C_6Cl_5CHCl_2 + C_6H_5\overset{\oplus}{C}H_2$$

$$C_6H_5\overset{\oplus}{C}H_2 + I^{\ominus} \longrightarrow C_6H_5CH_2I$$

The fact that perchlorotoluene does not yield pentachlorobenzylidene chloride with toluene in the absence of iodide ion, under the same reaction conditions, is inconsistent with such a mechanism.

Ionic mechanisms for the formation of perchlorobibenzyl may also be given. For example:

$$C_6Cl_5CCl_3 \longrightarrow C_6Cl_5\overset{\oplus}{C}Cl_2 + Cl^{\ominus}$$

$$C_6Cl_5CCl_3 + I^{\ominus} \longrightarrow C_6Cl_5\overset{\oplus}{C}Cl_2 + ClI$$

$$C_6Cl_5\overset{\oplus}{C}Cl_2 + C_6Cl_5\overset{\oplus}{C}Cl_2 \longrightarrow C_6Cl_5CCl_2CCl_2C_6Cl_5$$

and

$$C_6Cl_5CCl_3 + I^{\ominus} \longrightarrow C_6Cl_5\overset{\oplus}{C}Cl_2 + ClI$$

$$C_6Cl_5\overset{\oplus}{C}Cl_2 + C_6Cl_5CCl_3 \longrightarrow Cl^{\ominus} + C_6Cl_5CCl_2CCl_2C_6Cl_5$$

Regarding the second mechanism, the second step is extremely improbable because of the well-known high steric hindrance in the reactions at the *alpha* carbon atom of 2:6-dichlorophenyl derivatives.[22] This hindrance would, in this case, be in addition increased because of the large volume of the attacking perchlorobenzyl anion and also because of the internal steric strain of the perchlorobibenzyl. Moreover, the inertness of the trichloromethyl group towards nucleophilic displacements at the carbon atom is also well known.[10,23] Furthermore, it appears improbable that perchlorobenzyl anion would be stable enough in acetic acid solution to be such an effective intermediate.

As far as the first ionic mechanism is concerned, although it is known that the tendency of an α-chlorotoluene to give a carbonium ion increases with the number of chlorine atoms bonded to the *alpha* carbon atom,[24] in spite of the solvolysis of perchlorotoluene (presumably taking place by an S_N1 mechanism) is actually

[20] P. D. Bartlett and J. E. Leffler, *J. Amer. Chem. Soc.* **72**, 3030 (1950).
[21] H. Pines, D. R. Strehlau and V. N. Ipatieff, *J. Amer. Chem. Soc.* **71**, 3534 (1949).
[22] M. S. Reich, *Bull. Soc. Chim. Fr.* **21**, 217 (1917); G. Lock and F. Asinger, *Chem. Abstr.* **26**, 1910 (1932); G. Lock, *Ber.* **66**, 1527 (1933); S. D. Ross, *J. Amer. Chem. Soc.* **70**, 4039 (1948); S. D. Ross and M. Markarian, *Ibid.* **71**, 2756 (1949); S. J. Agyal, P. J. Morris, R. C. Rassack and J. A. Waterer, *J. Chem. Soc.* 2704 (1949); T. Alfrey and W. H. Ebelke, *J. Amer. Chem. Soc.* **71**, 3235 (1949); M. Ballester, *An. Real Soc. Españ. Fis. y Quim.* **50 B**, 765 (1954); P. G. Harvey, F. Smith, M. Stacey and J. C. Tatlow, *J. Appl. Chem.* **4**, 325 (1954).
[23] J. Hine, *Physical Organic Chemistry* p. 131. McGraw-Hill, New York (1956); M. Ballester, *Chem. Rev.* **55** 288, 289 (1955).
[24] E. D. Hughes, *Trans. Faraday Soc.* **38**, 625 (1941).

occurring under the reaction conditions, the required intermediate perchlorobenzyl anion makes it improbable.

No such ionic mechanisms can provide a reasonable account for the results of the reaction in the presence of toluene.

The possibility that perchlorobenzyl iodide could play a role as an intermediate cannot be ruled out. It is reasonable that perchlorobenzyl iodide would appreciably dissociate at the reaction temperature giving perchlorobenzyl radical. In fact, perchlorotoluene and 2:3:5:6-tetrachlorobenzotrichloride begin to decompose appreciably at temperatures as low as 185° and this fact has been attributed to an exceptionally facile homolysis of the carbon–chlorine bonds of the trichloromethyl group when flanked by two *ortho* chlorine atoms (steric strain).[25]

VOL. 6 1959

Moreover, in halides of comparable structures the dissociation energies of the carbon–iodine bonds are about 30 kcal smaller than those of the carbon–chloride bonds.[26] It could be expected therefore a low temperature of decomposition for the perchlorobenzyl iodide.

In view that solvolysis of perchlorotoluene occurs under the reaction conditions, perchlorobenzyl cation could account for the formation of perchlorobenzyl radical either by conversion into labile perchlorobenzyl iodide or by a direct electron-transfer reaction with iodide ion. As far as the mechanism of the formation of the perchlorobenzyl radical is concerned, the evidence here described does not allow any safe decision on the matter.

It has been found[27] that at 100° there is an attack of iodine on acetic acid with the formation of hydrogen iodide. The reaction of iodide with perchlorotoluene in aqueous acetic acid can therefore be explained as a reduction of perchlorotoluene by hydrogen iodide. The greatly increased yield of 2:3:4:5:6-pentachlorobenzylidene chloride may be due to the change in the nature of the iodide. Accordingly, it has been found[28] that hydrogen bromide in acetic acid reduces perchlorotoluene to pentachlorobenzylidene chloride exclusively.

CONFIGURATION AND RELATED STERIC INHIBITION PHENOMENA

Configurations for the stilbenes described have been made on the basis of their ultra-violet spectra.

In general, tri-conjugated *trans* forms absorb more and at longer wave lengths than the *cis* forms. The pair of unsubstituted stilbenes is an example.[29]

In order to apply the ultra-violet spectra to the configurations it was considered convenient to investigate first the spectra of the *cis*- and *trans*-α:α′-dichlorostilbenes which configurations have been well established by Bergmann by dielectric constant measurements.[30]

The absorption spectrum of *trans*-α:α′-dichlorostilbenes shows a general hypsochromic shift with respect to that of its *cis* isomer (Fig. 1a). Accordingly, the latter shows a maximum at longer wavelengths ($\lambda = 281$ mμ; $\varepsilon = 8950$) than the former ($\lambda = 270$ mμ; $\varepsilon = 11{,}400$). Similar anomalous behaviour has been recently found

[25] M. Ballester and C. Molinet, unpublished results.
[26] C. Walling, *Free Radicals in Solution* p. 50. Wiley, New York (1957).
[27] M. Ballester and J. Ros, unpublished work.
[28] M. Ballester and E. Guardiola, unpublished results.
[29] E. A. Braude and E. S. Waight, *Progress in Stereochemistry* (Edited by W. Klyne), Vol. 1, p. 126. Butterworths, London (1954).
[30] E. Bergmann, *J. Chem. Soc.* 402 (1936).

in α:α′-dialkylstilbenes:[31] the *trans* forms absorb *stronger* and at shorter wavelengths than the *cis* forms.

The anomalous spectra of the α:α′-dichlorostilbenes are attributable to steric inhibition to resonance. It is assumed that resonance in *cis*-stilbene—but not in its *trans* isomer—is sterically inhibited in some extent due to the impossibility of the two benzene nuclei and the central ethylene bond lying in the same plane.[29] By

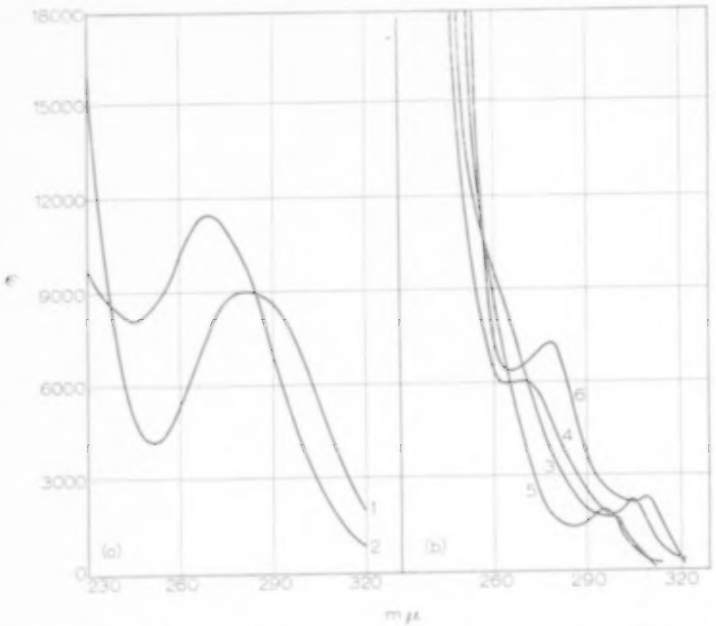

FIG. 1. *cis*-α,α′-→-dichlorostilbene, 1; *trans*-α,α′-dichlorostilbene, 2; *trans*-α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbene, 3; *cis*-α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbene, 4; *trans*-perchlorostilbene, 5; *cis*-perchlorostilbene, 6.

using Stuart atomic models it becomes clear that substitution of both ethylene hydrogen atoms by chlorine in stilbene prevents coplanarity in the *trans* form but leaves the *cis* form almost sterically undisturbed (Fig. 2). Such effect arises mainly from the interaction between the *beta* chlorine atoms and the *ortho* hydrogen atoms.

Accordingly, while the introduction of two *alpha* chlorine atoms in *cis*-stilbene produces practically no shift of the maximum of absorption and little change in the intensity of the low-frequency band, in the *trans*-stilbene it results in an important hypsochromic shift and a strong reduction of the intensity of absorption.*

In this connexion it has to be mentioned that the ultra-violet spectrum of the *trans*-α:α′-dichlorostilbene was recorded by Arends.[32] However, because its maximum lies closer to that of the *cis*-stilbene, he concluded, according to configurations found in the literature for the known α:α′-dichlorostilbenes,[33] that it was the *cis* isomer.

* *Cis*-stilbene; $\lambda = 280$ mμ; $\varepsilon = 9800$. *Trans*-stilbene; $\lambda = 294$ mμ; $\varepsilon = 27{,}600$.[31]

[31] H. Suzuki, *Bull. Chem. Soc. Japan* **25**, 145 (1952).
[32] B. Arends, *Ber.* **64 B**, 1936 (1931).
[33] A. Blanck, *Liebigs Ann.* **248**, 17 (1888); A. Eiloart, *Amer. Chem. J.* **12**, 231 (1890).

In this connexion it is convenient to indicate that the configurations found in the literature for the α:*o*:α′:*o*′- and α:*p*:α′:*p*′-tetrachlorostilbenes are probably wrong.[34]

In the cases of α:α′-dimethyl- and α:α′-diethylstilbenes, because of the larger sphere of action of the methyl and the ethyl groups, it can be expected—and it has

FIG. 2.

actually been found—that the absorption is hypsochromically shifted even in their *cis* forms.

It is reasonable to assume that a similar situation occurs in the case of the α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-decachlorostilbenes and the perchlorostilbenes, especially in the latter, where the strong *o*-H × α-Cl interactions in the *trans* forms are all replaced by the stronger *o*-Cl × α-Cl interaction. In fact, as in the case of the α:α′-dichlorostilbenes, the ultra-violet spectrum of the higher-melting decachlorostilbene shows, with respect to that of its lower-melting isomer, a general hypsochromic shift (Fig. 1b). This shift is greater in the perchlorostilbenes than in the decachlorostilbenes.

The bathochromic shift of the *cis*-perchlorostilbenes with respect to the *cis*-decachlorostilbene (Fig. 1b) may be ascribed to normal electronic effect due to the substitution.

The configurations thus assigned are consistent with those attributable by the melting point rule, i.e. *trans* configuration for the higher-melting isomeride.

Ultra-violet light usually converts the *trans* isomerides into their *cis* forms.[35]

[34] F. Fox, *Ber.* **26**, 653 (1893); J. Kenner and E. Witham, *J. Chem. Soc.* 1962 (1910); E. E. Fleck, *J. Amer. Chem. Soc.* **70**, 2173 (1948).
[35] L. Crombie, *Quart. Rev.* **6**, 101 (1952); G. M. Wyman, *Chem. Rev.* **55**, 625 (1955).

The convertions occur here in the opposite direction. These results are probably related to their anomalous ultra-violet absorption spectra. Solubilities may also play a role in such stereomutations by favouring the formation of the less soluble *trans* isomeride. In fact, in the case of the perchlorostilbenes practically all the *trans* form crystallises from solution during the illumination.

EXPERIMENTAL

Reaction of perchlorotoluene with potassium iodide

A mixture of perchlorotoluene[86] (1 g), potassium iodide (1·4 g), purified, glacial acetic acid (20 ml) and water (1 ml) was heated (steam-bath) under nitrogen, for 22·5 hr. The mass was then poured into water (200 ml), and after removal of the iodine with sodium bisulphite, it was heated (steam-bath) for half an hour. The suspension was cooled, shaken vigorously with ether (300 ml) and filtered. The insoluble part (0·287 g) consisted of pure trans-*perchlorostilbene*, m.p. ca. 400°. *Ultra-violet*: $\lambda = 296, 305\ m\mu$; $\varepsilon = 1{\cdot}8 \times 10^5, 2{\cdot}1 \times 10^5$. (Found: C, 28·1; H, 0·1; Cl, 71·6; *mol. wt.* (camphor) 578; $C_{14}Cl_{12}$ requires C, 28·3; H, 0·0; Cl, 71·7% mol. wt. 593·6).

The ether solution, after being extracted with sodium bicarbonate solution, gave cis-*perchlorostilbene* (0·377 g), m.p. 225–229°, which, after crystallisation from ethyl acetate, m.p. 230·0–231·5°. *Ultra-violet*: $\lambda = 279, 309\ m\mu$; $\varepsilon = 7{\cdot}2 \times 10^5, 2{\cdot}2 \times 10^5$. (Found: C, 28·3; H, 0·1; Cl, 71·8; mol. wt. (camphor) 570; $C_{14}Cl_{12}$ requires C, 28·3; H, 0·0; Cl, 71·7% mol. wt. 593·6). The ethereal mother-liquor gave on evaporation a solid residue (0·081 g), which after extraction with methanol was identified as 2:3:4:5:6-pentachlorobenzylidene chloride by m.p. and mixed m.p. with an authentic sample prepared by photo-chlorination of 2:3:4:5:6-pentachlorotoluene.[87] From the methanol solution more *cis*-perchlorostilbene (0·006 g) was obtained.

Attempted isomerisation of cis-*perchlorostilbenes with iodine*

A mixture consisting of *cis*-perchlorostilbene (0·1 g), iodine (0·04 g) purified acetic acid (7 ml) was heated (steam-bath) during 24 hr. The resulting mixture was poured into water, the iodine destroyed with sodium bisulphite solution and the heating continued for 45 min. Treatment with ether gave no insoluble residue. The ethereal layer was separated, washed with sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. Removal of the ether gave unchanged perchlorostilbene quantitatively, which was identified by m.p. and mixed m.p.

Attempted isomerisation of trans-*perchlorostilbene with iodine*

A mixture consisting of *trans*-perchlorostilbene (0·1 g), iodine (0·04 g) and purified acetic acid (7 ml) was treated as in the preceeding experiment. The solid obtained (0·093 g) was practically insoluble in ether, and was identified as *trans*-perchlorostilbene by m.p. and mixed m.p. The ethereal layer gave more *trans*-perchlorostilbene (0·002 g).

Reaction of perchlorotoluene and potassium iodide in the presence of toluene

A mixture of perchlorotoluene (2 g), potassium iodide (2·8 g), chromic acid-purified, glacial acetic acid (40 ml), water (2 ml) and purified toluene (10 ml) was heated (22 hr) at 100° under nitrogen. A mixture of water (200 ml) and ether (100 ml) was added to the product, the iodine destroyed with sodium bisulphite solution, and the mass filtered. The residue (0·308 g), was identified as *trans*-perchlorostilbene by chlorine analysis and mixed m.p. with an authentic sample.

The ethereal layer was washed with sodium bicarbonate solution, with water, and dried over sodium sulphate. The solvents were removed at 130° under reduced pressure. The product was distilled (3 mm at 130°) and 0·378 g of crude benzyl iodide distilled and was identified (83%).

The residue of the distillation was redistilled at 0·2 mm. The fraction 100–120° weighed 0·868 g and consisted of 2:3:4:5:6-pentachlorobenzylidene chloride. The residue (0·375 g) was *cis*-perchlorostilbene. These products were identified by mixed m.p. and chlorine analysis.

This reaction was repeated several times and the ratio of amounts of isomeric perchlorostilbenes remained constant (*cis*/*trans* = 1·2), close to the value obtained when the reaction was performed without toluene (1·3). The total yield of the reaction was always around 90 per cent.

[86] M. Ballester and C. Molinet, *Chem. & Ind.* 1290 (1954).
[87] G. Lock, *Ber.* **66**, 1527 (1933); M. Ballester, *Mem. Real Acad. Barcelona* **29**, 271 (1948).

Iodine and toluene under the conditions of the foregoing experiment

A mixture of iodine (0·69 g), potassium iodide (0·6 g), chromic acid-purified, glacial acetic acid (20 ml), purified toluene (5 ml) and water (1 ml) was heated at 100°, under nitrogen during 22·5 hr. No benzyl iodide was detected.

Perchlorotuene and iodine in aqueous acetic acid

A solution containing perchlorotoluene (0·1 g), purified iodine (0·069 g), chromic acid-purified, glacial acetic acid (2 ml) and water (0·1 ml) was heated in a sealed tube at 100° during 22·5 hr. The solid phase formed on standing was filtered and by treatment with ether was resolved into 0·016 g (21%) of *trans*-perchlorostilbene and 0·011 g (15%) of *cis*-perchlorostilbene.

The mother liquor was diluted with water, the iodine removed with sodium bisulphite, extracted with ether and decanted. The ethereal layer was washed with sodium bicarbonate solution, dried, and the ether removed. The residue (0·038 g) was digested in hot methanol leaving a residue (0·036 g, 40%) consisting of 2:3:4:5:6-pentachlorobenzylidene chloride which was identified by m.p. and mixed m.p. with an authentic sample.[37]

This experiment was repeated repurifying the starting materials and the results were reproduced.

Reaction of perchlorotoluene with ferrous chloride

A mixture of perchlorotoluene (0·5 g), $FeCl_2.4H_2O$ (1 g) and purified, glacial acetic acid (10 ml) was heated (steam-bath) for 8 hr. The separation of the reaction products was carried out as in the preceeding reaction and *cis*-perchlorostilbene (0·131 g) and *trans*-perchlorostilbene (0·199 g) were obtained. The yields were 32·5% and 49·3%, respectively. The products were identified by mixed m.p. with those obtained from the reaction of perchlorotoluene with potassium iodide.

Hydrolyses of perchlorotoluene with aqueous acetic acid

A solution of perchlorotoluene (0·2 g) in purified, glacial acetic acid (4 ml) was heated at 100° during three days. The solution was poured into water and strongly acidified with a few drops of mineral acid and heated (vapour bath) during 2 hr. The mixture was then extracted with ether, the ethereal layer extracted with sodium bicarbonate solution and discarded . The sodium bicarbonate solution was acidified with concentrated HCl and extracted with ether. Evaporation of the ether yielded 2:3:4:5:6-pentachlorobenzoic acid (0·104 g, 65%). It was identified by m.p. and mixed m.p. with an authentic sample.

A solution containing perchlorotoluene (0·2 g), purified, glacial acetic acid (5 ml) and water (0·2 ml), was heated at 100° during 22 hr. The resulting solution deposited on cooling perchlorotoluene (0·078 g). The mother-liquor was poured into water and then extracted with ether. The ethereal layer, after extraction with sodium bicarbonate solution, gave (0·094 g) which after crystallization from ethanol gave perchlorotoluene (0·057 g). The sodium bicarbonate solution was acidified with concentrated HCl and extracted with ether. Evaporation of the ether gave 2:3:4:5:6-pentachlorobenzoic acid (0·018 g) identified as above.

Perchlorotoluene in aqueous acetic acid containing toluene

A solution containing perchlorotoluene (0·5 g), purified, glacial acetic acid (10 ml), water (0·5 ml) and purified toluene (2·5 ml) was heated at 100°, during 22 hr. After evaporation of the acid perchlorotoluene (0·446 g) was recovered.

Reaction of perchlorotoluene with copper and pyridine

To an ice-cooled solution of perchlorotoluene (0·5 g) in pyridine (2 ml), freshly precipitated copper (0·095 g) was added. The mixture was heated (steam-bath) during an hour, acidified and heated again. The insoluble part was extracted in a Kumagava extractor with carbon tetrachloride for 25 hr, and *trans*-perchlorostilbene (0·17 g) was obtained. The mother liquor, after evaporation of carbon tetrachloride, gave a residue which, crystallised from ethyl acetate and yielded pure *cis*-perchlorostilbene. The reaction products were identified by m.p. and mixed m.p. with those obtained from the reaction of perchlorotoluene with potassium iodide.

VOL. 6 1959

Isomerisation of cis*-perchlorostilbene with ultra-violet light*

In a quartz vessel, a solution of *cis*-perchlorostilbene (0·1 g) in purified dioxane (5 ml) was illuminated during 5·5 hr with the ultra-violet radiation from a 500-watt mercury lamp situated at a distance of 20 cm. The solid phase formed was filtered (0·062 g) and consisted of *trans*-perchlorostilbene, identified by m.p. and mixed m.p.

Nuclear chlorination of trans*-α:α′-dichlorostilbene*

A solution of anhydrous aluminium chloride (0·04 g) in sulphuryl chloride (2 ml) was added gradually to a solution containing *trans*-dichlorostilbene[35] (0·05 g), sulphur monochloride (0·04 g), and sulphuryl chloride (2 ml). The resulting solution was gently refluxed during 2·5 hr and then concentrated to one-fourth its original volume. The mass thus obtained was treated, as usual, with warm water, sodium carbonate, and HCl. On filtration a residue (0·123 g) was obtained which after digestion with warm carbon tetrachloride gave an insoluble portion (0·048 g), which was identified as *trans*-perchlorostilbene by mixed m.p. and ultra-violet spectrum. Concentration of the carbon tetrachloride solution yielded another 0·006 g of the compound.

Attempted degradation of cis*-perchlorostilbene with chromic acid*

A mixture of *cis*-perchlorostilbene (0·073 g), chromic acid (0·5 g) and chromic acid purified acetic acid (10 ml) was refluxed during 20 hr. The resulting mixture was poured into water and extracted with ether (100 ml). The part soluble in ether (0·065 g) consisted of *cis*-perchlorostilbene identified by m.p. and mixed m.p.

Reaction of trans*-perchlorostilbene with zinc*

A mixture of *trans*-perchlorostilbene (0·1 g) zinc powder (1 g) and purified dioxane (50 ml) was refluxed during 24 hr. The mass was filtered hot and on cooling a white precipitate formed (0·02 g). The mother liquor gave on concentration 0·06 g of the product. The substance melted at 329–336°. It was purified by sublimation at 190° under 0·001 mm. The substance melted then at 345–348°. (Found: Cl, 67·6; $C_{14}Cl_{10}$ requires Cl, 67·8%).

Reaction of cis*-perchlorostilbene with zinc*

The quantities and conditions were the same as those stated in the preceding experiment. The resulting solution gave on cooling 0·05 g of fine needles, m.p. 260°. (Found: Cl, 55·2; $C_{14}H_4Cl_6$ requires Cl, 55·3%).

Attempted degradation of trans*-perchlorostilbene with fuming nitric acid*

A mixture of *trans*-perchlorostilbene (0·036 g), a droplet of mercury and fuming nitric acid (5 ml) was refluxed during 259 hr. The mixture was then poured into salted water, extracted with ether and filtered. The insoluble portion (0·033 g) was identified as *trans*-perchlorostilbene by m.p. and mixed m.p.

Attempted degradation of cis*-perchlorostilbene with fuming nitric acid*

A mixture of *cis*-perchlorostilbene (0·042 g), a droplet of mercury and fuming nitric acid (10 ml) was refluxed during 196 hr. The mass was poured into water and filtered. The residue, (0·036 g), was identified as *cis*-perchlorostilbene by m.p. and mixed m.p.

Reaction of 2:3:4:5*-tetrachlorobenzotrichloride with potassium iodide*

A mixture of 2:3:4:5-tetrachlorobenzotrichloride[37,39] (4 g), potassium iodide (8 g) and chromic acid-treated, glacial acetic acid (80 ml) was heated at 100°, in a sealed glass container, during 5 days. The mass was treated with water and the iodine formed titrated with standard sodium thiosulphate, 0·0174 equivalents being used up. The resulting mixture was then filtered and residue (3·369 g) was obtained which by treatment with cold petroleum ether gave a solution, A, and a residue, B.

[35] A. Blank, *Liebigs Ann.* **248,** 17 (1888).
[39] M. Ballester, *An. Real Soc. Españ. Fis. y Quím.* (*Madrid*) **50 B,** 765 (1954).

A, yielded (0·515 g) solids which was submitted to chromatographic purification with alumina grade A. Solid (0·333 g) was obtained, which after treatment with cold petroleum ether gave a residue (0·016 g) which consisted of trans-α:2:3:4:5:α′:2′:3′:4′:5′-*decachlorostilbene*, m.p. 250–254°. *Ultra-violet* data. $\lambda = 297$ mμ; $\varepsilon = 1{\cdot}7 \times 10^3$. (Found: C, 32·4; H, 0·4; Cl, 67·5; $C_{14}H_2Cl_{10}$: requires C, 32·1; H, 0·4; Cl, 67·6%) On evaporation to dryness the ethereal solution gave cis-α:2:3:4:5:α′:2′:3′:4′:5′-*decachlorostilbene* (0·317 g) m.p. 139–140°. *Ultra-violet*: $\lambda = 270$, 299 mμ; $\varepsilon = 6 \times 10^3$, $1{\cdot}6 \times 10^3$. (Found: C, 32·2; H, 0·7; Cl, 67·7; $C_{14}H_2Cl_{10}$ requires 32·1; H, 0·4; Cl, 67·6%).

On treatment with hot carbon tetrachloride, B (2·854 g) gave α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-*dodecachlorobibenzyl* (1·902 g), m.p. 250–251°. *Ultra-violet*: $\lambda = 295$, 305 mμ; $\varepsilon = 1{\cdot}8 \times 10^3$. (Found: C, 28·3; H, 0·4; Cl, 71·4; $C_{14}H_2Cl_{12}$ requires C, 28·2; H, 0·3, Cl, 71·4%). The soluble portion after treatment with carbon tetrachloride and petroleum ether, yielded dodecachlorobibenzyl (0·004 g) and *trans*-decachlorostilbene (0·065 g). The remaining mixtures, which contained the difficultly separable dodecachlorobibenzyl and *trans*-decachlorostilbene, were analysed for chlorine. On the basis of these analyses it was concluded that they contained dodecachlorobibenzyl (0·46 g) and *trans*-decachlorostilbene (0·22 g).

Reaction of α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-*dodecachlorobibenzyl with potassium iodide*

In a sealed glass container, under nitrogen, a mixture of 1·5 g (0·0025 mole) of α:α:2:3:4:5:-α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl, potassium iodide (6 g) and chromic acid-purified, glacial acetic acid (60 ml) was heated at 100° for 10 days. The mass was then treated with water and the free iodine titrated with sodium thiosulphate, 0·0039 equivalents being used. Filtration gave a precipitate (1·366 g) which was extracted with petroleum ether. The residue, after repeated recrystallisations from carbon tetrachloride gave *trans*-α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbene (0·052 g) identified by mixed m.p. and chlorine analysis (Found: Cl, 67·5; Calc. for 67·6%) and unresolvable mixtures (0·89 g). Part of these mixtures (0·650 g) were analysed for chlorine and the values found were between those calculated for the dodecachlorobibenzyl and *trans*-decachlorostilbene, and were probably mixtures of these two substances. Assuming the decachlorostilbenes are the sole reaction products from the amount of free iodine the composition of the inseparable mixture is dodecachlorobibenzyl (0·345 g) and *trans*-decachlorostilbene (0·542 g).

The portion soluble in petroleum ether (0·424 g), after filtration through activated alumina (0·394 g) and melted at 141–142°. It was identified as *cis*-α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbene by mixed m.p. and chlorine analysis.

Reaction of 2:3:4:5-*tetrachlorobenzotrichloride with ferrous chloride*

A mixture of 2:3:4:5-tetrachlorobenzotrichloride (4 g), $FeCl_2.4H_2O$ (4 g) and chromic acid-purified acetic acid (80 ml) was heated (steam-bath) during 17·5 hr. The mass was then poured into water, acidified with HCl, ether-extracted, and filtered. The insoluble portion (2·472 g) was recrystallised from boiling dioxane yielding α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-decachlorobibenzyl which was identified by m.p., mixed m.p. and chlorine analysis.

Isomerisation of cis-α:2:3:4:5:α′:2′:3′:4′:5′-*decachlorostilbene with ultra-violet light*

A solution of *cis*-α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbene (0·05 g) in purified carbon tetrachloride (1·5 ml) contained in a quartz vessel was illuminated, during 21 hr, with the ultra-violet radiation from a 500 W mercury lamp situated at a distance of 20 cm from the vessel. The solid phase formed was filtered (0·038 g) and melted at 245–246°. It was identified as *trans* isomer by mixed m.p. and ultra-violet spectrum.

On evaporation of the mother liquor a residue was obtained which after being washed with cold petroleum ether yielded *trans* isomer (0·015 g, 66·2%).

Attempted hydrolysis of α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-*dodecachlorobibenzyl*

A mixture of α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl (0·2 g) and acetic acid (15 ml) was refluxed during four days. The resulting mass gave on treatment with water and filtration 0·188 g unchanged material.

VOL. 6 1959

A mixture of finely ground α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl (0·225 g) and concentrated sulphuric acid (15 ml) was heated at 100° during 6·5 days. The mass was then treated with water and filtered, and, 0·224 g starting material was recovered, and identified.

Nuclear chlorination of α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl

A solution of anhydrous aluminum chloride (0·5 g) in sulphuryl chloride (80 ml) was added gradually to a refluxing mixture of α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl (0·5 g), sulphuryl chloride (80 ml) and sulphur monochloride (1 g). The resulting mixture was concentrated to about 40 ml and the heating continued for about 3 hr. It was concentrated further to 5 ml and treated with warm water, slight excess of powdered sodium bicarbonate, excess of HCl and filtered. The solid residue (0·494 g) after treatment with warm carbon tetrachloride, yielded insoluble *trans*-perchlorostilbene (0·419 g). Concentration of the carbon tetrachloride solution gave *cis*-perchlorostilbene (0·016 g) and an oily residue (0·059 g).

The *trans*-perchlorostilbene was identified by m.p. mixed m.p., chlorine analysis and ultra-violet spectrum. The *cis*-perchlorostilbene was identified by m.p., mixed m.p. and ultra-violet spectrum.

Ultra-violet spectra. A "Unicam" ultra-violet spectrophotometer, Mod. SP.500 was used. Benzene-free[40] *cyclo*hexane was used as a solvent. In the case of the unsubstituted α:α′-dichlorostilbenes the spectra were recorded also using purified, absolute ethanol. The *trans*-α:α′-dichlorostilbene was prepared from α:α:α′:α′-tetrachlorobibenzyl[41] by treatment with powdered zinc in boiling ethanol.[35] It melted at 142·5–143·0°.

The *cis*-α:α′-dichlorostilbene was prepared by thermal isomerisation of its *trans* isomer (heating at 280° during four hours in a sealed glass tube). It was purified by careful crystallisations from ethanol and chromatography using neutral alumina, grade A. It melted at 65·5–66·5°.[35]

Acknowledgements—The authors wish to acknowledge their gratitude to Dr. Juan Estevan, Head of the Analytical Section of this Department, for the semi-microanalyses. Also, they desire to express their undebtedness to Dr. Rufo Crespo, of the Patronato "Juan de la Cierva" (Barcelona), for the ultra-violet spectra.

[40] A. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy in Organic Chemistry* p. 262. Edward Arnold, London (1954).
[41] F. W. J. Taylor and A. R. Murray, *J. Chem. Soc.* 2078 (1938).

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VOL.
6
1959

STRUCTURE OF PIPERIDINO-HEXOSE-REDUCTONE

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Abstract—The structure of piperidino-hexose-reductone, first described by Hodge and co-workers, was clarified by degradation reactions. Dihydro-anhydro-piperidino-hexose-reductone, obtained from piperidino-hexose-reductone in a clear way, was synthesized by reacting 1-methyl-4-chloro-*cyclo*penten(1)-ol(2)-one(3) with piperidine.

OVER the past 5 years Hodge *et al.*[1,2] have described new types of reductones. Crystalline amino reductones, $R_2N{\cdot}C_6H_7O_3$, and their anhydro derivatives, $R_2N{\cdot}C_6H_5O_2$, were prepared quite generally from both aldo- and keto-hexoses in reaction with various neutral or basic secondary amine salts; a nitrogen-free crystalline reductone was obtained by the same reaction applied to L-rhamnose.[2,3] Investigations of the scope of the reaction, preparative conditions, and antioxidant properties of the reductones are reported elsewhere.[3,4,5] Clarification of structure has been confined to piperidino-hexose-reductone because experiments have shown that the other amino-hexose-reductones in all probability have analogous structures.

Piperidino-hexose-reductone (I) with the summation formula $C_{11}H_{17}NO_3$ reduces exactly two equivalents of iodine in acetic acid solution. The test of Weygand and Csendes[6] with titanium (IV) salt and pyridine is positive. Moreover, the following customary reagents for reductones are reduced in the cold: Tillmans reagent (2:6-dichlorophenolindophenol) in acid solution, methylene blue in alkaline solution, and silver nitrate in acid or ammoniacal solution. An aqueous solution of I gives no perceptible color with ferric chloride in acid solution. However, if the aqueous solution is buffered with sodium acetate, either before or after adding ferric chloride—or, if the test is conducted with alcoholic solutions—an intense Prussian blue color is formed. This color gradually disappears on standing.

PIPERIDINO-HEXOSE-REDUCTONE AND ITS DERIVATIVES

I Piperidino-hexose-reductone = N-[1-methyl-1,2,3-trihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2 or 3)

[1] J. E. Hodge and C. E. Rist, *J. Amer. Chem. Soc.* **75**, 316 (1953).
[2] J. E. Hodge and B. E. Fisher, *Chem. Engng. News* **32**, 1436 (1954); *Abstracts of Papers presented at the 125th Meeting of the Amer. Chem. Soc., Kansas City*, 1954, p. 4D. American Chemical Society; *Ibid.* 130*th Meeting of the Amer. Chem. Soc., Atlantic City*, 1956, p. 23D. American Chemical Society (1956).
[3] J. E. Hodge, E. C. Nelson and B. E. Fisher, *J. Amer. Chem. Soc.* In preparation.
[4] J. E. Hodge and C. D. Evans, *U.S.Pat.* 2806794. (September 17, 1957).
[5] C. D. Evans, H. A. Moser, P. M. Cooney and J. E. Hodge, *J. Amer. Oil Chem. Soc.* **35**, 84 (1958).
[6] F. Weygand and E. Csendes, *Ber. Dtsch. Chem. Ges.* **85**, 45 (1952).

II Piperidino-hexose-reductone mono-O-methyl ether (nonreducing) = N-[1-methyl-1:2-dihydroxy-3-methoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

IIa Piperidino-hexose-reductone mono-O-methyl ether (reducing) = N-[1-methyl-1-methoxy-2:3-dihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2 or 3)

III Piperidino-hexose-reductone di-O-methyl ether = N-[1-methyl-1:3-dimethoxy-2-hydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

IV Piperidino-hexose-reductone monoacetate = N-[1-methyl-1:2-dihydroxy-3-acetoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

V 1-Methyl-4-piperidino-*cyclo*pentanol-(2 or 3)

VI Anhydro-piperidino-hexose-reductone = N-[1-methylene-2:3-dihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2 or 3)

VIa Anhydro-piperidino-hexose-reductone monoacetate = N-[1-methylene-2-hydroxy-3-acetoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VIb Anhydro-piperidino-hexose-reductone mono-O-methyl ether = N-[1-methylene-2-hydroxy-3-methoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VII Dihydro-anhydro-piperidino-hexose-reductone = N-[1-methyl-2:3-dihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VIIa Dihydro-anhydro-piperidino-hexose-reductone monoacetate = N-[1-methyl-2-hydroxy-3-acetoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VIII Phenylhydrazine derivative of I, identical with the phenylhydrazine derivative of VI

VIIIa Mono-O-acetyl derivative of VIII

VIIIb Dihydro derivative of VIII

IX Hydrogenation product of VIII, $C_6H_9NO_2$

X Methylsuccinic acid

XI Citramalic acid

XII Methiodide of V

XIII Methylreductic acid

XIV 1-Methyl-4-chloro*cyclo*penten(1)-ol(2)-one(3)

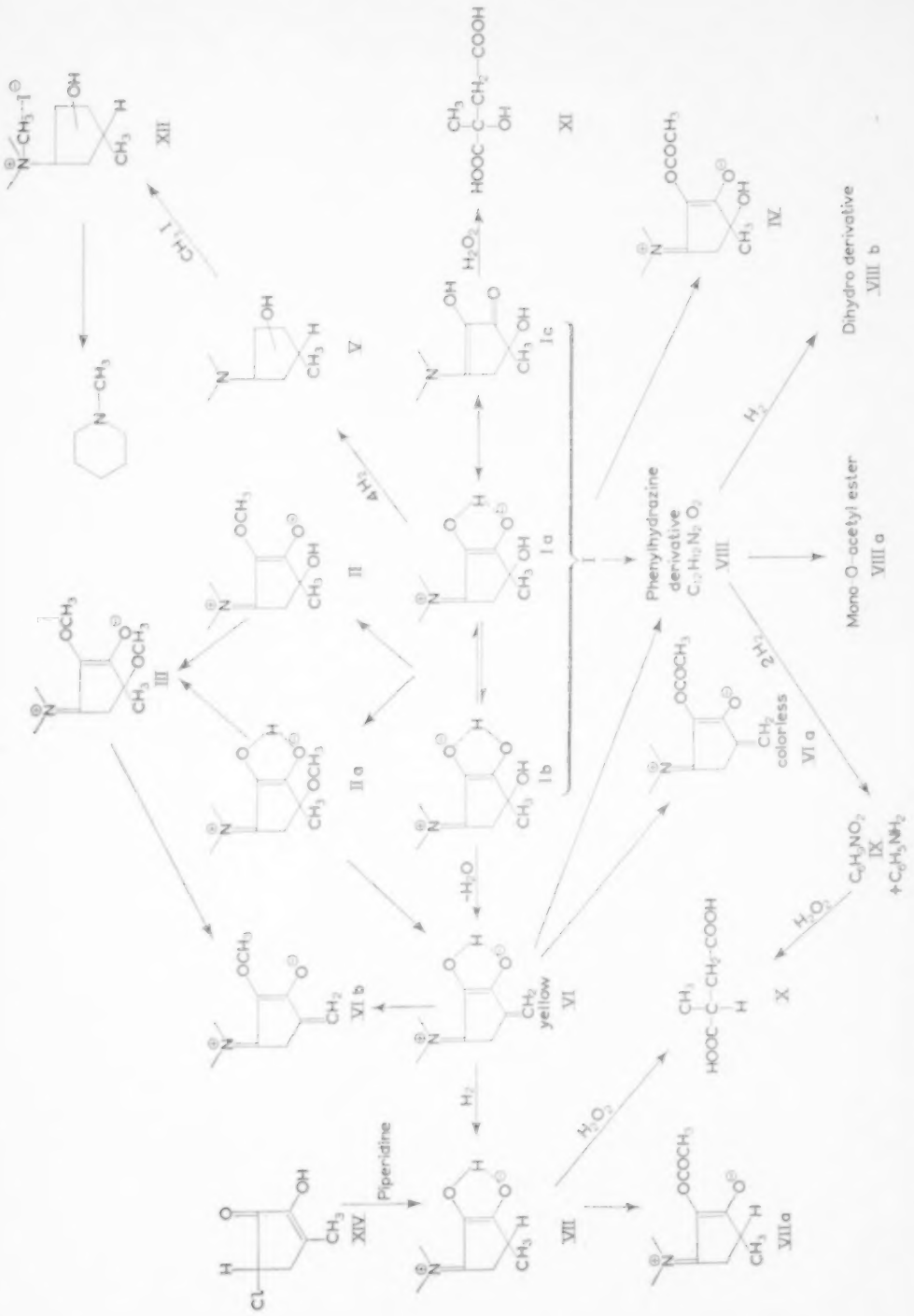
XV *Iso*methylreductic acid = 1-methyl-*cyclo*penten(1)-diol(2,4)-one(3)

XVI 1-Methyl-4-piperidino-*cyclo*penten(3)-ol(3)-one(2)

XVII Piperidino-hexose-reductone chloride hydrochloride = 1-methyl-1-chloro-2:3-dihydroxy-4-piperidino-*cyclo*pentadiene(2,4) hydrochloride

XVIII Anhydro-piperidino-hexose-reductone hydrochloride

VOL. 6 1959


Phenylhydrazine derivative $C_{12}H_{12}N_2O_2$ VIII
Mono-O-acetyl ester VIII a
Dihydro derivative VIII b
Piperidine
yellow
colorless
$C_6H_5NO_2$ IX
$+C_6H_5NH_2$

Piperidino-hexose-reductone contains one C-methyl group according to Kuhn–Roth oxidation results and the iodoform reaction.[2,3] The positive iodoform reaction also shows that the carbon atom adjacent to the methyl group bears oxygen.

Two hydroxyl groups are indicated by the preparation of two different mono-O-methyl ethers (II) and (IIa). The di-O-methyl ether (III) that is obtained directly from I or from either II or IIa by remethylation, is a neutral compound that cannot be further methylated. Because III also cannot be acetylated and shows no reaction with carbonyl reagents, it must be assumed that I possesses only two real hydroxyl functions. Because III is neutral, the third nonsubstitutable oxygen atom in III may be considered as an enolate anion that is neutralized within the molecule by the cationic nitrogen of the piperidino group. Therefore, an inner salt or betaine–like structure is indicated. Furthermore, because one of the two mono-O-methyl ethers (IIa) shows reductone reducing power, the third, nonsubstitutable oxygen and the amino or imino function must be capable of participation in the tripartite mesomeric reducing group.

Only one of the two hydroxyl groups of I that can be methylated is acetylated with acetic anhydride. The nonreducing mono-O-acetyl derivative (IV) is readily hydrolyzed in dilute acetic acid yielding I and indicating that IV is an enolic ester.

Piperidine is easily split from I by mineral acids and hot, strong alkali; therefore, the piperidino radical is in a labile configuration. During acid hydrolysis the N-free radical undergoes a yet unexplained transformation.

Piperidino-hexose-reductone is not hydrogenated at room temperature in alcohol or glacial acetic acid with reduced platinum dioxide catalyst. However, in mineral acid solution four moles of hydrogen are consumed, and a substance with the summation formula $C_{11}H_{21}NO$ (V) is formed; i.e. two hydroxyl groups are hydrogenolytically removed. One mole of methyl iodide is accepted by V to form the quaternary salt (XII), and N-methylpiperdine is obtained from XII by the Hofmann degradation. This result indicates that heterocyclic quaternary nitrogen is not present in the structure, as was previously suspected.

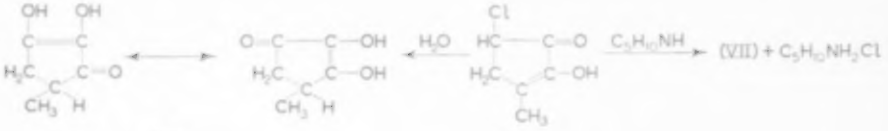
Upon heating in *n*-butanol that contains 10 to 15 per cent hydrogen chloride by weight, I is dehydrated. The acidic hydrochloride that crystallizes from the hot reaction mixture is converted by sodium acetate solution to the yellow, neutral compound (VI) with the summation formula $C_{11}H_{15}NO_2$. In contrast to I, VI takes up one mole of hydrogen very quickly at room temperature in glacial acetic acid with platinum or Raney nickel catalyst. If the hydrogenation is stopped here, an amino reductone with summation formula $C_{11}H_{17}NO_2$ (VII) is isolated. Both VI and VII show reductone–reducing power and give a deep-blue color with ferric chloride in alcoholic solution. C-methyl determinations according to Kuhn–Roth showed no methyl group in VI and one methyl group in VII.

Piperidino-hexose-reductone reacts with phenylhydrazine very slowly in acetic acid, but rapidly in hot mineral acid solution. Piperidine and water are split out, and a phenylhydrazone or phenylazo derivative (VIII), $C_{12}H_{12}N_2O_2$, is formed in 97 per cent of the theoretical yield. Two isomers can be separated by paper chromatography. These two interconvertible forms were isolated. The anhydro product (VI) reacts readily with phenylhydrazine in hot acetic acid solution to yield the same composite product (VIII) that is obtained from I.

By catalytic hydrogenation of VIII, aniline and a crystalline reductone with the summation formula $C_6H_8NO_2$ (IX) are formed. Aniline is split out also by the action

of sodium hydrosulphite on VIII. If the catalytic hydrogenation is stopped after one mole of hydrogen is taken up, a dihydro compound (VIIIb) $C_{12}H_{14}N_2O_2$ can be isolated. Oxidation of IX with hydrogen peroxide splits out carbon dioxide and yields methylsuccinic acid (X) which is obtained also from VII by oxidation with hydrogen peroxide. Oxidation of I with hydrogen peroxide yielded the highly significant degradation product $C_5H_8O_5$ which was isolated and identified as citramalic acid (XI); i.e. α-methyl-α-hydroxysuccinic acid. Oxidation of I with potassium permanganate or sodium hypobromite gave oxalic acid.

The finding of citramalic acid among the degradation products of piperidino-hexose-reductone and the isolation of methylsuccinic acid from the dihydro-anhydro derivative (VII) allows the supposition that piperidino-hexose-reductone contains the carbon skeleton of the cyclic "diketone" that Meyerfeld[7] discovered in beech tar oil. Rojahn and Rühl[8] showed that this compound is enolic and gave it the structure of 1-methyl-*cyclo*penten(1)-ol(2)-one(3). Hesse and Böckmann[9] synthesized the methyl-*cyclo*pentenolone and converted it by chlorination and hydrolysis to methylreductic acid (XIII). Then they oxidized methylreductic acid with silver oxide



XIII XIV

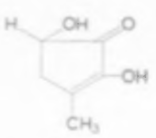
and obtained methylsuccinic acid (X). More recently Hesse and Brieg[10] have demonstrated a simple synthesis of methylreductic acid by halogenation of the methyl*cyclo*-pentenolone from wood tar. They showed Meyerfeld and Ohlgart's compound to be 1-methyl*cyclo*penten(3)-ol(3)-one(2) in aqueous solution, and the chloro compound obtained from it proved to be 1-methyl-4-chloro*cyclo*penten(1)-ol(2)-one(3) (XIV). Hydrolysis of XIV gave methylreductic acid in good yield. The structure of XIV was proved by synthesis and oxidative degradation.

A product identical with VII is obtained by the reaction of XIV with piperidine with the splitting out of hydrogen chloride. The identity of VII with the reaction product of XIV with piperidine was proved by analysis, melting point, mixed melting point, U.V. and I.R. spectrum, and by a Debye–Scherrer photograph of the crystalline powder. Particularly, the complete agreement of the two I.R. spectra in the so-called "fingerprint" region showed that the two products represent the same compound.

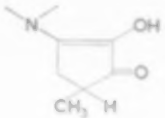
The position of the double bond in the dihydro-anhydro compound (VII) is not established by the synthesis. Since VII is a reductone like I, it must be assumed that the reaction between 1-methyl-4-chloro*cyclo*penten(1)-ol(2)-one(3) and piperidine occurs with a tautomeric rearrangement. Such a rearrangement occurs also during the preparation of methylreductic acid by saponification of XIV, according to Hesse, *et al.*[11] These authors isolated a nonreductone intermediate product that is isomeric

[7] J. Meyerfeld, *Chemikerztg.* **36**, 549 (1912).
[8] C. A. Rojahn and F. Rühl, *Ber. Dtsch. Pharm. Ges.* **264**, 211 (1926).
[9] G. Hesse and K. Böckmann, *Liebigs Ann.* **563**, 37 (1949).
[10] G. Hesse and K. Breig, *Liebigs Ann.* **592**, 120 (1955).
[11] G. Hesse, F. Exner and H. Hertel, *Liebigs Ann.* **609**, 57 (1957).

with methylreductic acid. For this isomer the structure of a 1-methyl*cyclo*penten(1)-diol(2,4)-one(3) (XV) was demonstrated. In view of the tautomeric shifts required by



XV

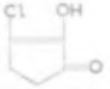


XVI

the conversion of XV to XIII, formulation of the dihydro-anhydro compound as VII, derived from XVI, is justified.

Betaine-like structures are proposed for I and VII on the basis of their high melting points and low solubilities in nonpolar solvents. Measurements of the dipole moments of VII in dioxane gave 5·0 *D* (Table 1).

TABLE 1. DIPOLE MOMENTS OF THE AMINO REDUCTONES AND RELATED SUBSTANCES IN DIOXANE

Experimentally determined moments		Estimated moments	
I	4·55 *D*	Ia	13–15 *D*
II	8·1 *D*	Ib	10 *D*
III	6·2 *D*	Ic	2·2 *D*
VI	5·9 *D*		
VII	5·0 *D*		2·4 *D*
	1·65 *D*		

Furthermore VII, VI, and I showed no true carbonyl band in the I.R. spectra. The sharp band at 1667 cm^{-1} for VII, at 1660 cm^{-1} for VI, and at 1680 cm^{-1} for I, is attributed to an enolized carbonyl group in a conjugated system.[12] A very broad band in the range 1520–1570 cm^{-1} for each of the three reductones probably arises from both C=C and C=N double bonds in the resonating system. Vinylogs of amides characteristically absorb at 1540 cm^{-1}.[12] Such a broad band is possible for a betaine-like structure. This interpretation is plausible also because, from the experimental findings, one oxygen function in I is neither hydroxyl nor carbonyl nor ether grouping, III is a neutral compound, and only one hydroxyl group in VI and VII can be acetylated or methylated. The results of further dipole measurements are tabulated in Table 1.

The value found for chloro*cyclo*pentenolone is smaller than the estimated value. That may have its basis in the fact that a planar five-membered ring was assumed in the estimation, and the moments of the polar group were projected in this plane. Therefore maximum values are obtained by calculation. The values found for I and

[12] N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, *J. Amer. Chem. Soc.* **71**, 3337 (1949).

VII lie far above those which were calculated from the formulations Ic and XVI. The O-methyl ethers II and III show dipolarity to even higher degree than I and VII. The methyl ethers would be expected to give moments of only 2 to 3 *D*, if they were derived from the structure Ic.

In addition to the keto structures Ic and XVI, a betaine-like formulation must be assumed as a further limiting form. However, the dipole moment found is significantly smaller than that calculated for a pure betaine form. More characteristic for this determination is the dielectric increment that was measured for I, II, and III (Table 2). The values found lie between 6 and 9 and therefore are much too small for a pure betaine structure. For example, Greenstein and Wyman[13] found a dielectric increment of 24·4 for *o*-amino*cyclo*hexane carboxylic acid, and 60 for the corresponding *meta* compound. Hence I and VII and their derivatives could not be correctly represented by a single formula. For example, it was obligatory to draw upon the three formulas Ia, Ib, and Ic to represent I.

VOL. 6 1959

TABLE 2. DIELECTRIC INCREMENTS OF I, II AND III IN 70 PER CENT ETHANOL

	$\delta\varepsilon/\delta c$
I	7·5 ± 1
II	6·1 ± 1
III	9·3 ± 1

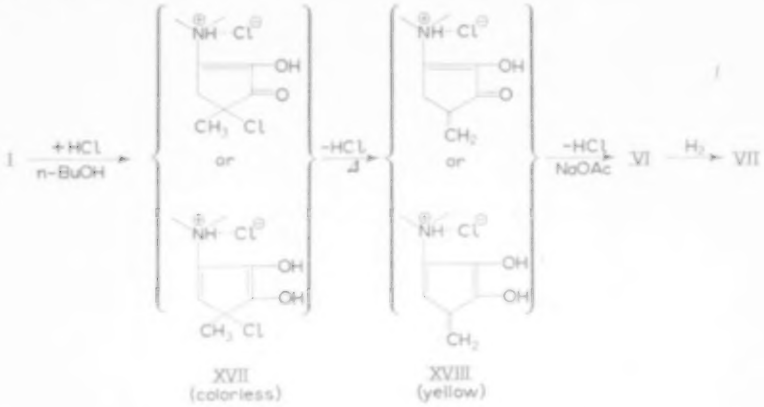
Whereas the position of the enolic hydrogen in the formulas for piperidino-hexose-reductone (Ia, Ib) is, of necessity, not fixed, one is obliged to determine the position of the enolic hydroxyl (enolate anion) in the enediol–inactive mono-O-methyl ether. The following arguments are given to substantiate formula II: (1) Periodate is rapidly consumed by II in aqueous solution at 0°, pH 4. A hydrolysis before the periodate oxidation is therefore improbable; and also because II, in contrast to I, does not form a phenylhydrazone even after long heating in mineral acid solution. (2) In agreement with the I.R. spectra of α:β-unsaturated β-tertiary aminoketones (Cromwell *et al.*[12]), II as well as I and VII shows a sharp band (keto) at about 1665 cm^{-1} and a broad band at 1515–1575 cm^{-1}. Cromwell found no such displacement of the carbonyl frequency for α-aminoketones. Therefore it is assumed that the potential carbonyl group stands in the β-position to the piperidino radical. (3) It is to be considered that a mesomerism in the sense of Ia$\leftrightarrow$ Ic is possible only when the methoxyl group is at C^3.

The same arguments hold for formulations of the mono-O-acetyl compounds, VIa and VIIa.

The relationship between VII and I is believed to be fixed by the several cycles of interconversions of I to VI (e.g. I $\rightarrow$ XVII $\rightarrow$ XVIII $\rightarrow$ VI; I $\rightarrow$ XVII $\rightarrow$ IIa $\rightarrow$ VI; I $\rightarrow$ II $\rightarrow$ VIb = I $\rightarrow$ III $\rightarrow$ VIb = I $\rightarrow$ IIa $\rightarrow$ III $\rightarrow$ VIb = I $\rightarrow$ VI $\rightarrow$ VIb) which were demonstrated step by step with isolation and analysis of each intermediate. For the demonstration of the relationship between I and VII, it is most important that the intermediate VI possesses a terminal methylene group as a consequence of splitting out the tertiary hydroxyl group with one hydrogen of the methyl group. No C-methyl

[13] J. P. Greenstein and J. Wyman, *J. Amer. Chem. Soc.* **60**, 2341 (1938).

group is present in VI according to the Kuhn–Roth determination, but it is present again after hydrogenation of VI to VII.



The colorless (XVII) and yellow (XVIII) hydrochlorides which were isolated are both strongly acidic and yield ionic chlorine in aqueous solution. The colorless chloride–hydrochloride (XVII) yields acetic acid by Kuhn–Roth oxidation (after precipitation of the chlorine with silver sulfate); therefore it retains the C-methyl group. When XVII is allowed to stand in methanol at 25°, the tertiary O-methyl ether (IIa) with reductone properties is obtained through its hydrochloride. A tertiary hydroxyl or chloride would be expected to methylate under these conditions. Methanol is eliminated from IIa by heating it in *n*-butanol-hydrogen chloride, thereby producing XVIII and VI. Likewise, methanol is eliminated from the di-O-methyl ether (III) to yield the same mono-O-methyl ether (VIb) that is obtained by direct methylation of VI, or by dehydration of II.

The formulated relationship of I, VI, and VII is supported also by their U.V. spectra. The principal maxima and extinction coefficents of the three substances in methanol are presented in Table 3.

TABLE 3. PRINCIPAL MAXIMA AND EXTINCTION COEFFICIENTS OF AMINO REDUCTONES IN METHANOL

Compound	λ_{max}	$E_{1\,cm}^{1\%}$
(I) piperidino-hexose-reductone	315	1510
(VI) anhydro derivative of I	360	1250
(VII) dihydro derivative of VI	315	1516

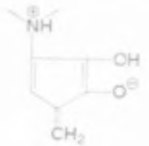
For a complete description of VI and XVIII, fulvene–betaine structures probably should be considered on the following grounds: Aside from the phenylhydrazine derivatives, only VI and XVIII of all the derivatives made are inherently colored. They show strong yellow color as do fulvenes. The test of Rosen[14] for nucleophilic aromatic

[14] M. J. Rosen, *Analyt. Chem.* **27**, 111 (1955).

nucleus is positive for VI. Different structure in I and VI is shown by titrations with Tillmans reagent. Although I reduces this reagent instantly in acid solution below pH 4, and also in alkaline solution, it reduces very slowly at pH 6 to pH 7 at 25°. Donation of a proton to either the nitrogen atom in Ic or to the oxygen atom in the betaine–like structures is doubtless a prerequisite for reductone formation from I. In contrast, VI reduces Tillmans reagent instantly in neutral aqueous solution, which indicates that the nitrogen or oxygen is more readily if not already protonated. After a few milliliters of Tillmans reagent (or iodine) is consumed, VI yields dark purplish-brown substance(s) in a manner resembling the behavior of pyrogallol under these conditions, and quantitative titration is thereby precluded. Finally, the empirical rule of Saytzeff dictates that the dehydration of I should involve one of the methylene, not methyl, hydrogens. Because methyl hydrogen definitely is involved, a tautomeric shift of one of the methylene hydrogens to the imino nitrogen (as in the lower formula of XVII) is postulated to precede the dehydrochlorination.

VOL. 6 1959

Nevertheless, these facts stand against the pure fulvene structure (XIX): (1) The mono-O-acetyl compound (VIa), isolated in 58 per cent yield, is colorless. (2) Only one active hydrogen was found by the method of Zerewitinoff. Also, by isotopic exchange experiments on VI in water that contained tritium, smaller tritium values than that calculated for one exchangeable hydrogen were always found. (3) In the region 900–1600 cm^{-1}, VI shows so many absorption bands that do not correspond with typical fulvene bands. The characteristic fulvene band at 900 cm^{-1} is observed, but against it the γ(CH) *cis* band of conjugated double bonds is not observed.



XIX

Investigation toward clarification of the mode of formation of I from C^{14}-labelled glucose are in progress at the Technische Universität of Berlin-Charlottenburg.

EXPERIMENTAL

Part I: By J. E. Hodge and B. E. Fisher

Piperidino-hexose-reductone mono-O-methyl ether (II). Piperidino-hexose-reductone, 4·23 g (20 mmoles), was slurried in dimethylsulphate, 4·1 g (30 mmoles), and 5 N sodium hydroxide, 6 ml (30 mmoles), was added dropwise with continual swirling of the mixture. The flask was cooled to keep the temp below 20°. After standing at 25° for 15 min, the clear, yellow solution was neutralized with a few drops of dilute sulphuric acid, then it was extracted with chloroform. Evaporation of the dried extracts gave a syrup which crystallized completely. Colorless prisms were obtained by recrystallization from 45 ml benzene, 3·5 g (77 per cent of theory), m.p. 140–142°. A second recrystallization from acetone gave the pure compound, m.p. 144°. (Found: C, 63·6; H, 8·50; N, 6·13; OCH_3, 14·9; $C_{13}H_{19}NO_5$ (225·28) requires: C, 63·97; H, 8·50; N, 6·22; OCH_3, 13·78%).

When 1 mole of II was treated with 4·6 moles sodium metaperiodate, it consumed 2·5 moles in 1 hr, 2·8 moles in 24 hr, 3·0 moles in 48 hr, and 3·1 moles in 72 hr. Formaldehyde could not be detected.

Kuhn–Roth analysis for C-methyl gave 1·0 mole of acetic acid per mole of compound. The iodoform test was positive, but the yield was low. Tillmans reagent was not reduced in dilute acetic acid. After hydrolysis in hot 2 N hydrochloric acid, Tillmans reagent was reduced. No hydrogen was

taken up in neutral aqueous solution with Adams platinum dioxide catalyst; however, when the solution was made 0·1 N with hydrochloric acid, 3·4 moles of hydrogen per mole of II was absorbed at 25°. The hydrogenated solution consumed periodate at 5° (3·3 moles in 6 hr) and yielded no formaldehyde. Ferric chloride gave a red-purple color.

Ultra-violet absorption measurements gave λ_{max} 299 mμ; $E^{1\%}_{1cm}$ 1530 in water and dilute alkali. In 0·1 N hydrochloric acid: λ_{max} 298 mμ; $E^{1\%}_{1cm}$ 1435.

A yellow *picrate* of II melted at 147°. (Found: N, 12·3 (Dumas) $C_{18}H_{22}N_8O_{16}$ requires: N, 12·32%).

Remethylation of II in dimethyl sulphate–sodium hydroxide gave the *di*-O-*methyl ether* (III), m.p. 58–59·5°, described below.

Piperidino-hexose-reductone di-O-*methyl ether* (III). Piperidino-hexose-reductone, 21·1 g (0·100 mole), was stirred in water under nitrogen at 5° while dimethyl sulphate, 50 g (0·39 mole), and 52 g of 50 per cent (wt/wt) sodium hydroxide (0·65 mole) were dropped simultaneously into the reaction mixture for 30 min. The clear solution was allowed to stand and warm to 18° for 2 hr. Methylation was then repeated by dropping 13 g of dimethyl sulphate (total, 0·50 mole) into the strongly alkaline solution while stirring it. After the solution had stood 16 hr at 25°, a syrupy product was isolated by chloroform extraction. It was dissolved in 200 ml of *n*-heptane at 85°. Filtration and cooling gave 22·2 g (two crops), 93 per cent of theory, m.p. 56°. One gram of the mono-O-ether (II) was removed from the crude product by fractional recrystallization from *n*-heptane. The pure *di*-O-*methyl ether* melted at 58–59·5°. (Found: C, 65·4; H, 8·86; N, 5·84; OCH_3, 26·1; $C_{13}H_{21}NO_6$ (239·31) requires: C, 65·24; H, 8·84; N, 5·85; OCH_3, 25·92%).

The compound was soluble in water and in organic solvents. The aqueous solution was neutral and did not reduce Tillmans reagent or hot Fehling solution. Addition of ferric chloride gave only a faint brownish-purple color. The iodoform test was negative. Hydrolysis in 2 N sulphuric acid at 100° produced a solution that reduced Tillmans reagent strongly at 25°.

The *di*-O-*methyl ether*, m.p. 58–59°, was formed also by methylation of IIa with dimethyl sulphate and sodium hydroxide. The mixed melting point with the product described above was not lowered.

Piperidino-hexose-reductone monoacetate (IV). Piperidino-hexose-reductone, 2·11 g, was suspended in 40 ml acetic anhydride and the mixture was heated at 65° for 15 min until a clear, nearly colorless solution was obtained. Storage of the solution at 0° for 2 days produced white crystals which were filtered off, washed with ether, and dried *in vacuo* at 56°; yield, 0·88 g, m.p. 170°. The filtrate was distilled under vacuum at 50° leaving a dry crystalline residue. Suspension of the residue in ether, storage at 0°, with isolation as before gave 1·62 g, m.p. 168–169°; total yield 2·50 g, 98 per cent of theory. Recrystallization from anhydrous ethyl acetate did not raise the melting point. Acetylation of I in pyridine at 25° with excess acetic anhydride gave the same compound in 92 per cent yield. (Found: N, 5·54; CH_3CO, 16·7; $C_{12}H_{19}NO_8$ (253·29) requires: N, 5·53; CH_3CO, 16·99%).

The *mono*-O-*acetyl* derivative did not reduce Tillmans reagent in 3 N acetic acid at 25°. However, after heating the acetic acid solution to 100° and cooling to 25°, it reduced Tillmans reagent instantly. When the heated acetic acid solution was neutralized with sodium hydroxide, I crystallized (56 per cent of theory); m.p. 230° (decomp), mixed m.p. with I not lowered.

The *acetyl* derivative in absolute ethanol gave a stable blue color with one drop of alcoholic ferric chloride solution. Tillmans reagent was not reduced. In absolute methanol and in acetate-buffered acetic acid solution (pH 4·6) the *mono*-O-*acetyl* derivative gave no deep color with ferric chloride solution; whereas I gave a deep blue color in parallel experiments under both conditions. In methanol Tillmans reagent was reduced and, also, the yellow color of added ferric chloride soon disappeared, indicating a reduction of ferric to ferrous ion.

Piperidino-hexose-reductone-hydrochloride. Piperidino-hexose-reductone, 8·5 g, was suspended in 25 ml absolute methanol under nitrogen, and 20 ml of a solution of hydrogen chloride (19 per cent wt/vol) in methanol was added. The clear yellow solution which formed was stored at 0°. Dilution with ether gave a colorless crystalline precipitate, 7·4 g, m.p. 120–121° (decomp with gas evolution). (Found: C, 53·38; H, 7·30; N, 5·69; $C_{11}H_{18}ClNO_5$ (247·72) requires: C, 53·33; H, 7·32; N, 5·65%).

Five grams of the hydrochloride was intimately mixed with 5 g of sodium acetate trihydrate, then 25 ml water was added under a nitrogen atmosphere. The crystalline form changed and, after standing at 25°, the precipitate was filtered off, washed with water and acetone, and dried. Yield 4·2 g, 98 per cent of theory, m.p. 229–231° (decomp); the mixed melting point of this compound with I was unchanged.

Piperidino-hexose-reductone chloride hydrochloride (XVII). Piperidino-hexose-reductone, 5·30 g, was suspended in 25 ml *n*-butanol and 50 ml of a cold solution of hydrogen chloride (21 per cent wt/wt) in *n*-butanol was added under nitrogen. After the clear yellow solution had warmed to 20° over 15 min, it was filtered, whereupon crystallization began in the filtrate. Dilution with ether, storage at 0°, filtration, followed by ether washing and drying, produced 5·65 g of white crystals, 85 per cent of theory, m.p. 167° (decomp). The product was purified by stirring it in 40 ml butanol–hydrogen chloride at 35° for 10 min, adding ether, cooling, and filtering as before. Yield 4·6 g, m.p. 168° (decomp). (Found: C, 50·4; H, 6·54; N, 5·29; Cl, 23·7; $C_{11}H_{17}Cl_2NO_5$ (266·17) requires: C, 49·63; H, 6·44; N, 5·26; Cl, 26·64%).

After precipitation of the chlorine with silver sulphate, Kuhn–Roth oxidation gave 0·5 mole of acetic acid per mole of compound. The compound (XVII) was not stable; it turned bright yellow in moist air and lost hydrogen chloride and turned brown on long storage in a desiccator over calcium chloride. Piperidino-hexose-reductone could not be recovered from the purified compound after neutralization with sodium acetate. The strongly acidic aqueous solution of XVII reduced Tillmans reagent instantly; and, when buffered with sodium acetate, it gave a deep blue-green color with ferric chloride solution.

Piperidino-hexose-reductone mono-O-methyl (and mono-O-ethyl) ether hydrochloride. Piperidino-hexose-reductone chloride hydrochloride (XVII), 10·0 g, was allowed to stand in 50 ml absolute methanol at 25° for several hr. The orange-colored solution was filtered then concentrated under vacuum to a crystalline residue which was rinsed onto a suction filter with ether. Dried *in vacuo* over calcium chloride for 48 hr, the product weighed 9·0 g, 93 per cent of theory, m.p. 138° (decomp). A sample that was recrystallized from methanol–hydrogen chloride–ether melted with decomposition at 144°. (Found: C, 55·08; H, 7·76; N, 5·35; $C_{12}H_{20}ClNO_5$ (261·75) requires: C, 55·06; H, 7·70; N, 5·35%).

A corresponding *mono-O-ethyl ether hydrochloride* was formed similarly by allowing XVII to stand in absolute ethanol for 1 hr at 25°; m.p. 142–143° (decomp). Yield, 60 per cent of theory. (Found: C, 56·65; H, 7·95; OC_2H_5, 15·6; $C_{13}H_{22}ClNO_5$ (275·77) requires: C, 56·62; H, 8·04; OC_2H_5, 16·33%).

Piperidino-hexose-reductone mono-O-methyl ether with reductone properties (IIa). The mono-O-methyl ether hydrochloride described in the preceding paragraph, 6·0 g, was partially dissolved in 15 ml cold water under nitrogen. Immediately thereafter 4·5 ml of 5 N sodium hydroxide was added to reduce the pH to 4. Stirring the clear, orange-red solution caused crystallization to occur, and 3·7 g of crude tan product was isolated. Two recrystallizations from benzene–light petroleum ether gave dense, colorless crystals, m.p. 153–154·5°. (Found: C, 64·17; H, 8·33; N, 6·12; OCH_3, 14·0; $C_{12}H_{19}NO_5$ (225·28) requires: C, 63·97; H, 8·50; N, 6·22; OCH_3, 13·78%).

This *mono-O-methyl ether* was more soluble in organic solvents and less soluble in water than II. Like I, it gave a neutral aqueous solution that reduced Tillmans reagent very slowly; however, when a drop of acetic acid was added to the blue solution, it turned red then decolorized immediately. The compound consumed exactly two equivalents of iodine in dilute acetic acid solution. Ferric chloride gave a Prussian blue color in ethanol, like I, but unlike II.

Conversion of mono-O-methyl ether (IIa) *to* VI *with loss of methanol.* The mono-O-methyl ether with reductone properties (IIa), 0·5 g, was dispersed in 3 ml *n*-butanol and 3 ml of a solution of hydrogen chloride (21 per cent wt/wt) in *n*-butanol was added. Heating until solution occurred followed by cooling gave a yellow *hydrochloride*, 0·35 g, m.p. 173–175° (decomp). Stirring the *hydrochloride* in 3 M sodium acetate solution, followed by recrystallization from acetone, gave bright yellow crystals, m.p. 196–197° (decomp), identical in all properties with VI. C-methyl determination by the method of Kuhn–Roth gave only a trace of acetic acid.

Anhydro-piperidino-hexose-reductone hydrochloride (XVIII). Piperidino-hexose-reductone, 320 g (1·51 moles), was suspended in 250 ml *n*-butanol and 1490 g of a cold solution of 10 per cent (wt/wt) hydrogen chloride in *n*-butanol was added while stirring under nitrogen atmosphere. The reductone partially dissolved in the cold then crystallized as the colorless chloride–hydrochloride (XVII) m.p. 168° (decomp). Upon heating the mixture with steam to 55° in 8 min, XVII dissolved; then, at 60–65° (10–12 min) a second *hydrochloride*, yellow in color, began to crystallize from solution. The reaction mixture was held at 66–70° for 15 min, then it was cooled rapidly to 22° and filtered. The filter-cake was washed with butanol, then with ether, and dried in a vacuum desiccator over calcium chloride to constant weight; yield 285 g, 82 per cent of theory. A sample of the product, recrystallized from

VOL. 6 1959

methanol–hydrogen chloride–ether, melted at 175–182° with decomposition. (Found: C, 58·0; H, 7·10; Cl, 15·3; $C_{11}H_{14}ClNO_2$ (229·70) requires: C, 57·51; H, 7·02; Cl, 15·44%).

This *hydrochloride*, in contrast to XVII, was quite stable (unchanged after standing 3 years in a screw-capped vial). The *picrate* salt of VI, m.p. 166°, also was stable.

Anhydro-piperidino-hexose-reductone (VI). The hydrochloride of anhydro-piperidino-hexose-reductone (XVIII), 275 g (1·20 moles) was stirred with 1 liter of water under nitrogen at 25° while a filtered solution of 204 g sodium acetate trihydrate (1·50 moles) in water was rapidly run in through a large-bore tube with outlet under the surface of the stirred mixture. Rapid and thorough stirring was continued for 30 min after neutralization (pH 4·5). The yellow crystalline precipitate was filtered off with suction, washed with five 200 ml portions of water, and dried over calcium chloride in vacuum desiccators to constant weight. Yield 226 g, 97·5 per cent of theory; m.p. 188–191° (decomp). This product was recrystallized from 1·75 liters of absolute ethanol; the solution was filtered through a steam-heated funnel before crystallization. A second recrystallization of 207 g from 2·25 liters of absolute ethanol gave glistening yellow flakes from which ethanol evaporated very slowly in air. Drying at 75° in a vacuum oven gave 172 g, opaque, straw-like crystals, m.p. 197–198° (decomp). A third recrystallization from acetone gave glistening yellow prismatic needles of the same melting point. (Found: C, 68·40; H, 7·82; N, 7·19; mol. wt. (Signer) 213; $C_{11}H_{15}NO_2$ (193·24) requires: C, 68·37; H, 7·82; N, 7.25%). One active hydrogen was shown at 23° and 95° by the method of Zerewitinoff.

Only 0·06 mole of acetic acid was produced per mole of VI by the Kuhn–Roth oxidation. Tillmans reagent and iodine were reduced instantly in neutral aqueous solution as well as in dilute acetic acid; however, dark oxidation products formed and prevented quantitative titration. The enediol reaction with titanium trichloride in methanol and in pyridine according to Weygand and Csendes[6] was positive. Ferric chloride gave a deep blue color which rapidly disappeared, leaving a dark red-brown solution.

Two absorption maxima were observed in the ultra-violet: In methanol: λ_{max} 360, 230; $E^{1\%}_{1cm}$ 1250, 684, respectively. In *iso*-octane: λ_{max} 358, 228. In water: λ_{max} 353, 228 (absorptions rapidly lost). In 0·1 N hydrochloric acid: λ_{max} 330; $E^{1\%}_{1cm}$ 1310. In 0·1 N sodium hydroxide λ_{max} 400; $E^{1\%}_{1cm}$ 342 (rapidly lost). Infra-red absorptions showed a sharp band at 1660 cm^{-1} and a broad band at 1525–1575 cm^{-1}. No band was evident in the true carbonyl range.

Anhydro-piperidino-hexose-reductone mono-O-methyl ether (VIb). Anhydro-piperidino-hexose-reductone, 4·83 g (25 mmoles), was suspended and stirred in freshly distilled dimethyl sulphate, 12·6 g (100 mmoles), at 5° under nitrogen. Sodium hydroxide, 16 ml of 6 N (96 mmoles), was dropped into mixture while keeping the reaction temp below 30°. After stirring for 1 hr at 25°, the amber-coloured solution was extracted repeatedly with chloroform. The combined extracts were back-extracted with water, then dried over sodium sulphate, and distilled. Water was added to the syrupy distillation residue to produce the hydrated crystals described below, 9·4 g, m.p. 66–68·5°. Drying over phosphorus pentoxide in a vacuum desiccator at 25° for several days gave anhydrous crystals, 4·4 g, 85 per cent of theory, m.p. 58–60°. Remethylation with methyl sulphate-sodium hydroxide, and also with methyl iodide–silver oxide, gave only *mono-O-methyl ether*, m.p. 58–60°. (Found: C, 69·65; H, 8·25; N, 6·76; OCH_3, 15·3; $C_{12}H_{17}NO_2$ (207·26) requires: C, 69·54; H, 8·25; N, 6·76; OCH_3, 14.97%).

Kuhn-Roth analysis for C-methyl gave only 0·13 mole of acetic acid per mole of compound. An aqueous solution of the ether was neutral, did not reduce Tillmans reagent, and gave no deep color with ferric chloride.

Piperidino-hexose-reductone mono-O-methyl ether (II) *hydrochloride*. Ten millimoles of II, 2·25 g, was dissolved in 15 ml of a *n*-butanol solution that contained 19 per cent hydrogen chloride (wt/vol). The mixture warmed spontaneously, and soon after solution white crystals separated. After standing overnight, the crystals were drawn off, washed with *n*-butanol, then with ether. Yield, 0·5 g, m.p. 148–149° (decomp, with reddening before melting). (Found: C, 54·8; H, 7·72; OCH_3, 12·18; $C_{12}H_{20}NO_2Cl$ (261·75) requires: C, 55·06; H, 7·70; OCH_3, 11·85%).

An aqueous solution of the compound was strongly acidic, gave a precipitate of silver chloride with silver nitrate solution, did not reduce Tillmans reagent, and gave a purple color with ferric chloride, the same as the color given by II. Treatment with sodium acetate solution gave II, m.p. 143–144°.

Anhydro-piperidino-hexose-reductone mono-O-methyl ether (VIb) *formed from* II *and from* III. Ten millimoles of II, 2·25 g, was suspended in 25 ml *n*-butanol and 25 ml of a *n*-butanol solution that contained 19 per cent hydrogen chloride (wt/vol) was added. The solution was heated on a steam bath under reflux for 1 hr; then the clear, orange solution was concentrated under vacuum. Crystallization occurred during concentration. Dilution with ether, filtration, and drying produced 2·05 g of crude hydrochloride which was recrystallized from ethanol–ether–hydrogen chloride; recovery 1·40 g, m.p. 140–142° (decomp). The hydrochloride was stirred in 10 ml 3 M sodium acetate solution, yielding 1·25 g of air-dried crystalline product. Recrystallization from water gave glistening flakes of a colorless, hydrated compound, m.p. 69·0–69·5°. (Found: C, 48·86; H, 9·13; N, 4·69; OCH_3, 10·77; H_2O (by drying under vacuum over P_2O_5 at 25°), 30·24; $C_{12}H_{17}NO_5{\cdot}5H_2O$ (297·34) requires: C, 48·47; H, 9·15; N, 4·71; OCH_3, 10·44; H_2O, 30·29%).

The hydrated crystals readily lost all water upon storage in a vacuum desiccator over a dehydrating agent. A clear liquid formed on applying vacuum. When dry, the liquid could be induced to crystallize completely by rubbing, m.p. 57–59·5°. When a few drops of water were added, the crystalline pentahydrate regenerated immediately. This cycle of drying and rehydration was repeated twice without significant loss.

In the same way this peculiar *pentahydrate* was formed starting with the di-O-methyl ether, III. Sixty mg of recrystallized *pentahydrate*, m.p. 68·5°, was produced from 0·33 g of III. (Found: C, 48·7; H, 9·24; N, 4·55; OCH_3, 9·44; H_2O, 30·97%).

The *pentahydrates* from II and from III were shown to be identical with that formed directly by methylation of VI by the method of mixed melting point. Also, a mixture of anhydrous crystals from II, III, and VI showed no lowering of the melting point.

Anhydro-piperidino-hexose-reductone monoacetate (VIa). Anhydro-piperidino-hexose-reductone, 1·93 g, was dissolved in 25 ml acetic anhydride at 25°. Two ml dry pyridine was added, and the solution was stored at 0° for 2 days. Distillation of the solvent under vacuum, with several additions of anhydrous ethyl acetate, gave a syrupy residue which, upon dilution with anhydrous ether, produced a crystalline product, 1·35 g, m.p. 81–83°, 58 per cent of theory. Two recrystallizations from petroleum ether gave the pure compound as dense, colorless prisms, m.p. 83°. (Found: C, 66·76; H, 7·22; CH_3CO, 17·8; $C_{12}H_{17}NO_5$ (235·27) requires: C, 66·36; H, 7·28; CH_3CO, 18·30%).

When acetylation was tried in the usual way, i.e. pouring the pyridine-acetic anhydride solution into ice water, VI was recovered in nearly quantitative yield. The acetyl derivative dissolved quickly in ether, benzene, and ethyl acetate. Tillmans reagent was reduced in both methanol and dilute acetic acid, leaving a brown-discolored solution. The blue color produced with ferric chloride rapidly turned to orange-brown in the manner noted for VI.

Kuhn–Roth oxidation gave 0·96 mole of acetic acid per mole of compound arising from the O-acetyl radical, indicating the absence of a C-methyl group on the 5-carbon ring.

Dihydro-anhydro-piperidino-hexose-reductone (VII). In a 300 ml stainless steel hydrogenation bomb, 19·3 g (0·10 mole) of VI, 135 ml of absolute ethanol, and 3 g of Raney nickel catalyst were shaken under 1,300 lb/in² hydrogen pressure for 1 hr at 25°. After filtration and concentration of the filtrate under vacuum (nitrogen atmosphere), a syrup was obtained which crystallized completely upon stirring vigorously with ether. The residue when filtered off, washed with ether, and dried, yielded 18·1 g, (93 per cent of theory) m.p. 151–153°. Two recrystallizations from absolute ethyl acetate (88 per cent recoveries) gave a pure, colorless compound, m.p. 154–155°.

The same compound was prepared by hydrogenation in glacial acetic acid (or absolute ethanol) at 25°, 45 lb/in² hydrogen pressure, Adams platinum dioxide catalyst. Yield, 75 per cent of theory. (Found: C, 68·0; H, 8·72; N, 7·17; mol. wt. 195 (by iodine titration); $C_{11}H_{17}NO_5$ (195·25) requires: C, 67·66; H, 8·78; N, 7·17%).

The dihydro compound reduced two equivalents of Tillmans reagent in acetic acid solution. Like I, it gave a blue color with ferric chloride in ethanol, or in acetate-buffered dilute acetic acid. The test of Weygand and Csendes[6] with titanium chloride in pyridine and in methanol was positive. Kuhn–Roth oxidation gave 0·5 mole of acetic acid per mole of compound.

The ultra-violet absorption curves for VII were virtually duplicates of the corresponding curves for I. In methanol: λ_{max} 315 mμ; $E^{1\%}_{1cm}$ 1516. In water: λ_{max} 305; $E^{1\%}_{1cm}$ 778. In 0·1 N hydrochloric acid: λ_{max} 298; $E^{1\%}_{1cm}$ 1277. In 0·1 N sodium hydroxide: λ_{max} 345; $E^{1\%}_{1cm}$ 335 (rapidly lost). The infra-red absorption curve showed a sharp band at 1667 cm^{-1} and a broad band at 1520–1580 cm^{-1} with no absorption in the true carbonyl range.

Dihydro-anhydro-piperidino-hexose-reductone monoacetate (VIIa). Following the acetylation procedure prescribed for VI, VII yielded colorless crystals after two recrystallizations from *n*-heptane, m.p. 92°, 47 per cent of theory. (Found: C, 66·2; H, 7·90; CH_3CO, 17·5; $C_{12}H_{19}NO_5$ (237·29) requires: C, 65·80; H, 8·07; CH_3CO, 18·14%).

Phenylhydrazine derivative of piperidino-hexose-reductone (VIII). Phenylhydrazine hydrochloride, 3·00 g (21 mmoles), was dissolved in 250 ml water at 80°. Under an atmosphere of nitrogen 4·23 g (20 mmoles) of I was added to the stirred aqueous solution, and the reaction mixture was held at 80–83° for 2 hr until the acidic solution had become nearly neutral and nonreducing toward Tillmans reagent. The deep red crystalline product was filtered off with suction and washed with hot water. The dried substance weighed 4·20 g, 97 per cent of theory, m.p. 202–204°. Two recrystallizations from 100 volumes of acetone gave straw-like, opaque, deep yellow needles, m.p. 205°. Brilliant deep red prisms, m.p. 204–205°, formed from alcohol. However, when these thick prisms were finely pulverized, the color was deep yellow. They gave no lowering of the melting point with the opaque crystals from acetone. Both recrystallized products gave a single, yellow-fluorescing spot under ultra-violet light (of the same R_F after paper chromatography in butanol–acetic acid–water; cf. VIII in Part II). Both products had the same analysis: (Found: C, 66·7; H, 5·58; N, 13·0 (Dumas); $C_{12}H_{12}N_2O_2$ (216·23) requires: C, 66·65; H, 5·59; N, 12·96%).

Kuhn–Roth oxidation gave 0·94 mole of acetic acid per mole of compound, indicating the presence of one C-methyl group. The iodoform test was negative. Reaction with sodium hydrosulphite in aqueous ethanol at 85° gave 80 per cent of the theoretical amount of aniline, isolated as benzanilide, m.p. 161°. The mixed melting point with an authentic sample was 161°.

Phenylhydrazine derivative of anhydro-piperidino-hexose-reductone (VIII). Anhydro-piperidino-hexose-reductone (VI) was reacted as described in the preceding paragraph with phenylhydrazine hydrochloride, producing 76 per cent of the theoretical amount of VIII, identical in all properties and in C, H, N, and C-methyl analyses with the $C_{12}H_{12}N_2O_2$ compound described above. The same compound was obtained in nearly quantitative yield from the reaction of VI with phenylhydrazine in 3 N acetic acid solution. In acetic acid under these conditions, I reacted very slowly and only a small amount of the red product was formed. The crude products showed both types of spots described for the paper chromatography of VIII in Part II. After recrystallization, only the slower moving, yellow-fluorescing spot was obtained.

Mono-O-acetyl ester of VIII (VIIIa)

Acetylation of VIII with a 4-molar excess of acetic anhydride in pyridine at 25° gave two *mono-O-acetyl* derivatives of different melting points. The lower melting ester crystallized from the reaction mixture within a few min. Upon recrystallization from ethanol it melted at 120–121°. The higher melting ester was more soluble in the reaction mixture but was less soluble in ethyl acetate. Repeated recrystallization from ethyl acetate gave brilliant yellow, felted needles, m.p. 177°. Both esters gave the same analyses within the experimental error: (Found: C, 65·02; H, 5·48; CH_3CO, 16·2; $C_{14}H_{14}N_2O_3$ (258·27) requires: C, 65·10; H, 5·46; CH_3CO, 16·67%).

Acetylation of the crude red product, that gave two spots by paper chromatography gave proportionately more of the lower melting acetate.

Part II: By F. WEYGAND, H. SIMON and W. BITTERLICH

Hydrogenation of piperidino-hexose-reductone to 1-*methyl*-4-*piperidino-cyclopentanol*-(2 *or* 3) (V). Platinum dioxide (200 mg) was prehydrogenated in a hydrogenation vessel. A solution of 4·22 g I (20 mmoles) in 100 ml 2 N sulphuric acid was run into the vessel along with a stream of hydrogen. After 20 hr at room temp 95 per cent of the calculated amount of hydrogen for 4 moles per mole of I was absorbed. The filtrate from the catalyst was stirred with barium carbonate until it became alkaline. After the addition of dilute sodium hydroxide, the solution was extracted with ether. Upon distillation of the ether the product partially volatilized and separated in the form of colorless crystals in the condenser. However, 1·2 g of the crystalline material remained in the distillation flask. After sublimation the purified product melted at 71°. (Found: C, 71·94; H, 11·36; N, 7·66; $C_{11}H_{21}NO$ (183·29) requires: C, 72·06; H, 11·55; N, 7·64%).

One active hydrogen was shown by the method of Zerewitinoff. The substance is extremely volatile and, for example, cannot be dried at room temp *in vacuo* over phosphorus pentoxide.

Methiodide (XII) *and Hofmann degradation of* V. One g V was heated with a tenfold excess of

methyl iodide in 20 ml nitromethane under reflux. After distillation of the nitromethane and recrystallization of the product, the m.p. was 142°. (Found: N, 4·42. $C_{12}H_{24}INO$ (325·23) requires: N, 4·31%).

For the Hofmann degradation, 1 g of the quaternary iodide (XII) was transformed to the free base with silver oxide. The solution was frozen and then dried. The residue was decomposed at 150° to yield N-*methyl-piperidine* by distillation. The base was isolated as the *picrate*, m.p. 148°. (Found: N, 16·76; $C_{12}H_{16}N_4O_7$ (328·28) requires: N, 17·05%).

Phenylhydrazine derivative of piperidino-hexose-reductone (VIII). Piperidino-hexose-reductone (4·22 g, 20 mmoles) was dissolved in 110 ml 1 N hydrochloric acid and 4·30 g phenylhydrazine was added. Phenylhydrazine hydrochloride separated at first but later dissolved upon warming. At about 70° the phenylhydrazone separated in the form of glittering orange-colored leaflets. Upon further warming the crystals became darker in color and were transformed to needles. After 10 min standing in a boiling-water bath, the deep red crystalline mass was filtered off, washed with dilute hydrochloric acid, and then with water. Yield 4·23 g, 97 per cent of theory.

Chromatographic investigations on paper showed that the product obtained consisted of a mixture of two forms. One form showed an R_F value of 0·76 in butanol–acetic acid–water (4 : 1 : 1) and fluoresced in ultra-violet light. The orange-coloured product that was obtained by short heating of the reaction mixture at 70° consisted preponderantly of this form (R_F 0·76), m.p. 189°. The other form showed an R_F value of 0·83 and absorbed ultra-violet light. By recrystallization from nitrobenzene or acetoacetic ester, the form of R_F 0·83 was obtained as yellow- or orange-colored crystals, preponderantly. The melting point and mixed melting point of these differently recrystallized products were the same: 194°. (Found: C, 66·48; H, 5·68; N, 13·02; mol. wt., 230·7; Calc. for $C_{12}H_{12}N_4O_2$: C, 66·65; H, 5·59; N, 12·96%, mol. wt., 216·23).

Hydrogenation of the phenylhydrazine derivative of piperidino-hexose-reductone (VIII → IX). A suspension of VIII, 8 g, in 150 ml of 80 per cent alcohol was hydrogenated with platinum (from 150 mg PtO_2) in a shaking vessel. After uptake of 800 to 900 ml of hydrogen within 2 to 3 hr, the rate of hydrogenation decreased. All substance had dissolved after 3 to 4 days. After an additional day hydrogenation was stopped. The solution was filtered from the catalyst and evaporated under nitrogen. Upon taking up the hydrogenated product in hot water, the incompletely hydrogenated substance remained undissolved. The filtrate was again concentrated *in vacuo* under nitrogen, and the residue was recrystallized from acetone, yielding 2 to 3 g of colorless to weak yellow leaflets, m.p. 200–202°.

Paper chromatography with *n*-butanol–acetic acid–water (4 : 1 : 1) showed the main product at R_F 0·67. A small amount of a second, enediol-active product was detected at R_F 0·81.

Only 3 hr were required when the hydrogenation was repeated at 60°.[15] The yield of crude, cream-colored product was 90 per cent of theory. Two recrystallizations from 125 volumes of acetone (75 per cent yields) gave the colorless product of m.p. 200–203°. (Found: C, 56·60; H, 7·04; N, 11·0; $C_6H_9NO_2$ (127·14) requires: C, 56·68; H, 7·13; N, 11·02%).

The compound reduced two equivalents of iodine in dilute acetic acid solution and gave Prussian blue color with ferric chloride in ethanol.

Dihydro derivative of VIII (VIIIb). Four g VIII was heated in 150 ml 80 per cent ethanol until dissolved. After cooling, a part of the substance separated as dark red crystals. The mixture was hydrogenated at room temp with 100 mg platinum dioxide. Under these conditions the suspended material dissolved completely, and a yellow precipitate formed after the uptake of 1 mole of hydrogen. The hydrogenation vessel was evacuated and filled with nitrogen. By decanting under a bell jar of nitrogen, the catalyst was separated, and the product was filtered off and dried. (Found: C, 65·62; H, 6·73; N, 12·68; $C_{12}H_{14}N_2O_2$ (218·25) requires: C, 66·04; H, 6·44; N, 12·84%).

Oxidation of IX *to methylsuccinic acid.* One millimole of IX (127 mg) was dissolved in 50 ml water by heating. While the solution was kept hot, 4 millimoles of hydrogen peroxide in the form of a 3 per cent solution was dropped in. After about 4 hr standing at 40–50°, the residue obtained by evaporation was extracted with acetone, and after repeated drying it was sublimed at 1 mm. The monoammonium salt of *methylsuccinic acid* so obtained ($C_5H_{11}NO_4$) was dissolved in dilute hydrochloric acid. After distilling off the acid, the dry residue was extracted with anhydrous acetone to yield the free *methylsuccinic acid.* Sublimation gave the pure acid, m.p. 112°. (Found: C, 45·37; H, 6·03; $C_5H_8O_4$ (132·11) requires: C, 45·46; H, 6·06%).

[15] By E. C. Nelson of the American Group.

Identity with *methylsuccinic acid* was proved by melting point, mixed melting point with authentic material and also by preparation of an anil (m.p. 104–106°) and a β-napthylimide (m.p. 160–161°).

Oxidation of VII *to methylsuccinic acid.* After dissolving 1·3 millimoles of VII in hot water and treating with 0·6 ml 30 per cent hydrogen peroxide solution, the reaction mixture was held for 10 min in a boiling-water bath. Gas was eliminated and the solution turned yellow. Evaporation under vacuum, addition of dilute hydrochloric acid, and reconcentration under vacuum gave a residue which was taken up in acetone; the piperidine hydrochloride was removed by filtration, the acetone evaporated, and the residue sublimed to yield *methylsuccinic acid*, m.p. 112°, identical with the product described in the preceding section.

Oxidation of piperidino-hexose-reductone to citramalic acid. Ten g I was dissolved in 300 ml water by heating. The solution was treated at 90° with 23 ml of 30 per cent hydrogen peroxide solution and was kept hot on the water bath for 30 min. Carbon dioxide was eliminated. After cooling, 30 g lead acetate was added. The precipitate which formed over 24 hr was dried and finely pulverized in a mortar. A strong stream of hydrogen sulphide was led into an aqueous suspension of this material for 2 hr. After filtering from the lead sulphide and evaporating under vacuum, the syrupy residue was taken up in 50 ml water. Di*cyclo*hexylamine was added to a significant alkaline reaction, then the excess amine was removed by extraction with petroleum ether. The syrup obtained after evaporation of the aqueous solution under vacuum crystallized after 2 days (8·9 g). The dried material was extracted once at the boiling point with 20 ml benzene and then was further extracted five times with 50 ml portions of benzene. The crystalline precipitates that formed in the various fractions during storage in the ice chest were dried and their melting points determined. Crystals from the second and third fractions were recrystallized from benzene (m.p. of the di*cyclo*hexylamine salt 137–140°). The free acid was obtained as a syrup by dissolving the salt in water and shaking with the acid form of a cation-exchange resin. Crystallization occurred upon cooling in ether to −78° and rubbing. After two recrystallizations from a mixture of ethyl acetate–petroleum ether (2 : 1), pure *citramalic acid* was obtained, m.p. 117°.

The melting point of a mixture of the oxidation product with synthetic *citramalic acid* was not lowered. Also, the melting points and mixed melting points of the di*cyclo*hexylamine salts, obtained by degradation of I, and the synthetically produced reference compound were not lowered (137–140°). (Found: C, 40·76; H, 5·60; $C_5H_8O_5$ (148·11) requires: C, 40·54; H, 5·44%).

Reaction of 1-*methyl*-4-*chloro*cyclo*penten*(1)-*ol*(2)-*one*(3) *with piperidine.* The chloro derivative of methyl *cyclo*pentenolone (XIV), 4·47 g, was dissolved in 30 ml benzene and this solution was dropped slowly into 40 ml piperidine that was held in an ice-salt mixture. After standing for 2 hr at room temp, the crystalline mass was drawn off by suction, and the filtrate was evaporated *in vacuo* under nitrogen between 35 and 40°. The residue was stirred with water; then filtration and recrystallization from a mixture of benzene-ligroin (2 : 3) gave the desired product, m.p. 153·5°, in yield better than 75 per cent of theory.

To compare this synthetic material with the dihydro-anhydro-piperidino-hexose-reductone (VII), both preparations were sublimed at 1 mm. (Found: C, 67·95; H, 8·90; N, 7·49; $C_{11}H_{17}NO_2$ (195·25) requires: C, 67·66; H, 8·78; N, 7·17%).

The mixed melting point of a mixture of VII and the synthetic material showed no depression. Also, the Debye–Scherrer photograph and the I.R. spectrum are exactly identical with those of VII.

The same compound was obtained in an analogous way from 1-methyl-2:3-diketo-4-chloropentane[16] and piperidine.

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SYNTHESE DU 1:6-ANHYDRO-GALACTOSE

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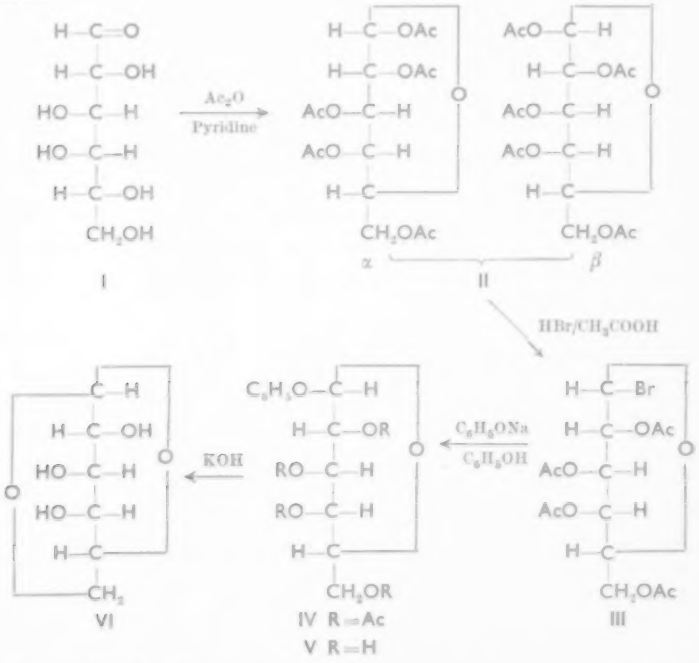
Abstract—1:6-anhydro-β-D-galactopyranose has been synthesised from galactose in a 70 per cent yield. Purification of intermediate derivatives was made unnecessary.

Résumé—La synthèse du 1:6-anhydro-β-D-galactopyranose a été réalisée avec un rendement global de 70% à partir de galactose et sans isolement des produits intermédiaires.

VOL. 6 1959

ETANT donné l'intérêt que présente le 1:6-anhydro-β-D-galactopyranose (VI) comme produit de départ pour la synthèse de dérivés du galactose et de la galactosamine[1], nous avons cherché à mettre au point une méthode permettant d'obtenir cette substance relativement facilement et avec un rendement convenable. En effet, jusqu'à présent, le 1:6-anhydro-galactose nécessaire pour ces travaux a été préparé par pyrolyse du lactose.[2] Si cette méthode est simple et le matériel de départ peu coûteux, le rendement en est faible. Il est donc exclu de l'utiliser, par exemple, pour la préparation de dérivés marqués par le carbone 14 devant servir à l'étude du métabolisme de ces carbohydrates.

Le schéma de synthèse que nous avons adopté comporte les stades suivants, à partir du galactose:



* Massachusetts General Hospital, Boston 14, Mass.

[1] R. W. Jeanloz et P. J. Stoffyn, *J. Amer. Chem. Soc.* **76**, 5682 (1954); R. W. Jeanloz, *Ibid.* **76**, 5684 (1954); R. W. Jeanloz, D. M. Schmid et P. J. Stoffyn, *Ibid.* **79**, 2586 (1957).

[2] R. M. Hann et C. S. Hudson, *J. Amer. Chem. Soc.* **64**, 2435 (1942).

Afin d'améliorer le rendement, tout en simplifiant les manipulations, nous avons étudié les divers stades séparément de manière à éviter l'isolement des produits intermédiaires. Par cette séquence, basée essentiellement sur l'hydrolyse alcaline du β-phényl-galactoside (V),[3] il est possible de préparer le 1:6-anhydro-galactose (VI) avec un rendement global de 70% à partir du galactose et sans purification des produits intermédiaires.

Le procédé le plus direct pour préparer le β-phényl-tétra-acétyl-galactoside (IV) consiste à chauffer le β-penta-acétyl-galactose (II) avec le phénol en présence d'une quantité catalytique d'acide *p.* toluènesulfonique.[4] Cette méthode présente toutefois l'inconvénient d'exiger la séparation préalable des penta-acétates anomères par cristallisation, l'isomère β, obtenu dans le cas le plus favorable avec un rendement de 50%,[5] étant seul utilisable. D'autre part, même en présence d'une quantité réduite d'acide *p.* toluènesulfonique, il y a anomérisation et une importante proportion d'α-phényl-tétra-acétyl-galactoside, inutilisable dans la suite, est formée. En conséquence, le passage du galactose au β-phényl-tétra-acétyl-galactoside ne peut se faire par cette voie qu'avec un rendement de l'ordre de 25% seulement. Pour cette raison, nous avons adopté le schéma décrit plus haut qui comporte un intermédiaire supplémentaire, l'α-acétobromogalactose (III), mais qui permet une augmentation considérable du rendement. En effet, la forte acidité du milieu au cours de la réaction entre le penta-acétyl-galactose et l'acide bromhydrique favorise l'anomérisation et la formation prépondérante de la forme stable du dérivé halogéné, en l'occurrence l'isomère α, aussi bien à partir d'α que de β-penta-acétate.[6]

Nous avons donc acétylé le galactose par l'anhydride acétique dans la pyridine, ce qui permet par simple distillation sous vide des solvants d'obtenir le mélange des penta-acétates qui est traité directement par l'acide bromhydrique. L'α-acétobromogalactose est obtenu après évaporation sous vide de l'excès de réactif avec un rendement supérieur à 90% en produit recristallisé.

Le produit brut, cristallin, (Rdt.: 97–98%), peut d'ailleurs être employé directement pour la préparation du β-phényl-tétra-acétyl-galactoside.

Cette transformation a été essayée par la réaction de l'α-acétobromogalactose avec le phénol en présence d'oxyde ou de carbonate d'argent selon la méthode de Koenigs–Knorr.[7] Diverses modifications[8] ont été apportées aux conditions expérimentales mais le rendement est resté inférieur à 50%.

Nous avons alors essayé le procédé de Michael,[9] soit la réaction de l'acétobromogalactose avec le phénate de potassium dans diverses conditions.[10] Les rendements ont été très faibles.

Finalement en utilisant le phénol lui-même comme solvant, en présence de phénate de potassium et en ajustant les quantités de réactifs de manière à maintenir le mélange réactionnel à l'état liquide à température ordinaire, nous avons pu obtenir le β-phényl-tétra-acétyl-galactoside avec un rendement de 64%. Au cours de cet essai,

[3] E. M. Montgomery, N. K. Richtmyer et C. S. Hudson, *J. Amer. Chem. Soc.* **65**, 3 (1943).
[4] B. Helferich, *Ber.* **77**, 194 (1944).
[5] F. J. Bates, and Associates, *Polarimetry, Saccharimetry and the Sugars* p. 488. National Bureau of Standards Circular C440, Washington (1942).
[6] E. Fischer, *Ber.* **44**, 1898 (1911).
[7] W. Koenigs et E. Knorr, *Ber.* **34**, 957 (1901).
[8] D. D. Reynolds et W. L. Evans, *J. Amer. Chem. Soc.* **60**, 2559 (1938); C. M. McCloskey, R. E. Pyle et G. H. Coleman, *J. Amer. Chem. Soc.* **66**, 349 (1944).
[9] A. Michael, *Amer. Chem. J.* **1**, 305 (1879).
[10] J. H. Fisher, W. L. Hawkins et H. Hibbert, *J. Amer. Chem. Soc.* **62**, 1412 (1940).

l'excès de phénol et le phénate de potassium ont été éliminés du mélange réactionnel, dilué dans le benzène, par lavage au moyen d'une solution aqueuse glacée d'hydroxyde de potassium à 10%. Or, nous avons constaté d'une part que le β-phényl-tétra-acétyl-galactoside pur soumis à ce traitement ne peut pas être récupéré entièrement, vraisemblablement par suite de la saponification partielle de groupements acétyle. D'autre part en hydrolysant directement le β-phényl-tétra-acétyl-galactoside (IV) par l'hydroxyde de potassium,[11] sans séparer le β-phényl-galactoside (V) intermédaire, nous avons obtenu le 1:6-anhydro-galactose (VI) avec un rendement de l'ordre de 90%.

Dans ces conditions, afin d'éviter les pertes dues au lavage du β-phényl-tétra-acétyl-galactoside en milieu fortement alcalin, nous n'avons pas isolé ce produit à l'état pur. Nous avons simplement neutralisé l'excès de phénol par la quantité stoechiométrique d'hydroxyde de potassium en solution aqueuse et extrait le produit par le benzène. Après évaporation du solvant, le β-phényl-tétra-acétyl-galactoside brut a été hydrolysé par l'hydroxyde de potassium 1·3 N.

Le mélange fut ensuite débarassé des ions potassium, de l'acide acétique et du phénol par passage sur deux colonnes de résines échangeurs d'ions: Permutit 50 et Déacidite 851. Par concentration sous vide de l'effluent neutre, le 1:6-anhydro-galactose fut obtenu avec un rendement de 72% à partir de l'acétobromogalactose.

PARTIE EXPERIMENTALE

α-*Acétobromogalactose* (III). Un mélange de 1.8 g de galactose, 13 ml de pyridine anhydre et 9 ml d'anhydride acétique est secoué pendant 24 h à température ordinaire dans un ballon de 250 ml. La solution homogène est laissée en repos pendant 12 h, puis les solvants sont éliminés par plusieurs codistillations sous pression réduite en présence de toluène, la température du bain de chauffage ne dépassant pas 60°. Le résidu sirupeux, étalé en couche mince sur les parois du ballon et débarassé sous vide plus poussé (0·5 mm Hg) des dernières traces de toluène, est dissous à température ordinaire dans 9 ml d'une solution saturée à 0° d'acide bromhydrique dans l'acide acétique glacial par agitation très énergique du ballon fermé. La mise en solution est complète après 30 à 60 minutes et le mélange est gardé deux heures en tout. Les acides sont évaporés sous vide par codistillation répétée en présence de toluène, la température du bain de chauffage restant inférieure à 50°. Le résidu sirupeux complètement séché sous vide plus poussé, est dilué par 1 ml d'éther et le ballon fermé est placé en glacière à −18°; l'α-acétobromogalactose cristallise. Après évaporation de l'éther, le produit brut pesant 4·0 g fond à 75–81° et est employé directement pour la suite de la préparation.

Un produit plus pur fondant à 79–81° est obtenu avec un rendement de 95% en filtrant la solution éthérée à l'abri de l'humidit.

1:6-*Anhydro*-β-D-*galactopyranose* (VI). 4·1 g d'α-acétobromogalactose brut sont dissous sous forte agitation dans une solution de 2·7 g de phénate de potassium sec* dans 27 g de phénol fondu à 40°. Le mélange, gardé à l'état liquide pendant 16 h à température ordinaire, est ensuite traité par une solution glacée de 16 g d'hydroxyde de potassium dans 160 ml d'eau pour neutraliser le phénol. Le β-phényl-tétra-acétyl-galactoside brut est extrait rapidement par trois portions de 75 ml de benzène. L'extrait benzénique, séché sur sulfate de sodium anhydre, est concentré sous vide et le résidu sirupeux jaune pâle pesant 6·6 g et contenant encore une petite quantité de phénol est hydrolysé par chauffage à reflux pendant 9 h avec une solution de 17 g d'hydroxyde de potassium dans 220 ml d'eau. Les ions potassium sont éliminés par passage sur une colonne de résine Permutit 50 (H^+), l'acide acétique et le phénol sont retenus ensuite sur une colonne de Déacidite 851 (OH^-).† L'élution

* Le phénate de potassium préparé par neutralisation de phénol avec la quantité stoechiométrique d'hydroxyde de potassium en solution aqueuse, est obtenu à l'état sec par élimination de l'eau en distillation azéotropique avec benzène.

† Nous tenons à remercier la Maison Philips et Pain pour le don gracieux des résines échangeurs d'ions.

[11] G. H. Coleman, C. M. McCloskey et R. Kirby, *Industr. Engng. Chem.* **36**, 1040 (1944).

de l'anhydro-galactose est contrôlée par le test de Molish. Par évaporation de l'éluat neutre on obtient 1·15 g de 1:6-anhydro-β-D-galactose cristallin fondant à 220–221°. Rendement: 72%.

L'anhydro-galactose peut être obtenu sous forme de dérivé acétoné par agitation pendant 24 h à température ordinaire avec 100 ml d'acétone et 10 g de sulfate de cuivre anhydre. Après filtration et évaporation du solvant, le résidu est repris par le chloroforme, la solution filtrée est concentrée et le 1:6-anhydro-3:4-*iso*propylidène-β-D-galactopyranose fondant à 151–152° est obtenu avec un rendement de 55% (calculé à partir du galactose).

Des rendements équivalents ont été obtenus à partir de 18 g de galactose.

Remerciements—Nous remercions vivement Monsieur le Professeur R. H. Martin ainsi que Monsieur le Docteur R. W. Jeanloz pour l'intérêt qu'ils ont manifesté pour ce travail.

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CHEMISTRY OF THE PODOCARPACEAE—I

CONSTITUENTS OF THE HEARTWOOD OF *PODOCARPUS SPICATUS*

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(*Received* 10 *November* 1958)

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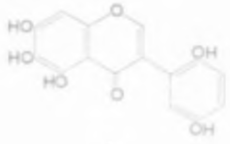
Abstract—Quercetin and a new *iso*flavone, podospicatin, have been isolated from *Podocarpus spicatus*. Podospicatin trimethyl ether has been shown to be 5:6:7:2′:5′-pentamethoxy*iso*flavone.

The heartwood of *Podocarpus spicatus* (Maori name—"Matai") has already been shown to contain the lignans, matairesinol,[1,2] conidendrin[3] and a third constituent, m.p. 212°.[1,3,4] While working on the mother liquors for a further supply of the third component, quercetin has been isolated in small yield.

The third compound has now been shown to be a new *iso*flavone, podospicatin, $C_{17}H_{14}O_7$. Podospicatin contains two methoxyl groups while complete methylation affords podospicatin trimethyl ether indicating the partial structure, $C_{15}H_5O_2(OCH_3)_5$, for the trimethyl ether. Spectral properties of podospicatin (λ_{max} 262, 302 mμ)[5] indicate an *iso*flavone structure which has been confirmed by degradation.

Mild alkaline hydrolysis of the trimethyl ether with ethanolic potassium hydroxide gave a phenol, $C_{14}H_7O_2(OCH_3)_5$, in high yield, the loss of one carbon atom being accounted for by the isolation of formic acid. More vigorous alkaline treatment afforded two fragments, an acid, identified as the dimethyl ether of homogentisic acid by comparison with a synthetic sample, and a phenol, agreeing in properties with those of antiarol (3:4:5-trimethoxyphenol). Podospicatin can thus be formulated as a dimethyl ether of 2′:5:5′:6:7-pentahydroxy*iso*flavone (I) and the product from mild alkaline treatment of the trimethylether as the benzyl ketone (II).



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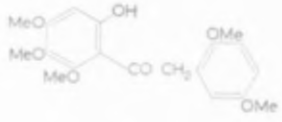

II

In only four cases has the 2′:5′-hydroxylation pattern been noted in naturally occurring flavones and this is the first record in an *iso*flavone.

EXPERIMENTAL

Microanalyses were carried out by Dr. A. R. Campbell, University of Otago. Ultra-violet spectra were measured in ethanol.

Isolation of podospicatin. The mother liquors from the crystallization of matairesinol[1] were

[1] L. H. Briggs, D. A. Peak and J. L. D. Woolloxall, *J. Proc. Roy. Soc. N.S.W.* **69**, 61 (1935).
[2] R. D. Haworth and T. Richardson, *J. Chem. Soc.* 633 (1935).
[3] R. D. Haworth, T. Richardson and G. Sheldrick, *J. Chem. Soc.* 1576 (1935); L. H. Briggs and D. A. Peak, *J. Chem. Soc.* 724 (1936).
[4] H. V. Brewerton, *New Zealand J. Sci.* **1**, 220 (1958).
[5] W. K. Warburton, *Quart. Rev.* **8**, 67 (1954).

evaporated, the residue finely ground and suspended in dilute sodium carbonate solution. Acidification of the filtered solution gave a black viscous product which was dissolved in hot alcohol (charcoal). After some weeks the deposited crystalline material was filtered, washed with alcohol and repeatedly crystallized from acetic acid to give podospicatin, pale yellow needles, m.p. 214–216°.

(Found: C, 61·9; H, 4·3; OMe, 18·8; Calc. for $C_{17}H_{14}O_7$: C, 61·8; H, 4·2; 2 OMe, 18·8%.)

Ultra-violet spectrum: λ_{max} 262 mμ (log ε 4·37), 302 mμ (log ε 4·11).

Isolation of quercetin. The alcoholic mother liquors from which podospicatin had been obtained were allowed to dry spontaneously. The residue was alternately crystallized from acetic acid (60%) and aqueous ethanol (50%) to give quercetin, m.p. and mixed m.p. 314–314·5°. The acetate[6] had m.p. 190–191°.

Bromopodospicatin. A solution of bromine (188 mg) in ethylene dibromide (11 ml) was added to a solution of podospicatin (200 mg) in the same solvent (49 ml). Extraction with sodium hydrogen carbonate solution (4 × 25 ml), followed by acidification, afforded material (2·0 mg) crystallizing from acetic acid (60%) in yellow needles, m.p. 202°.

(Found: C, 49·4; H, 3·4; Br, 19·2; Calc. for $C_{17}H_{13}O_7Br$: C, 49·9; H, 3·2; Br, 19·6%.)

Podospicatin trimethyl ether. Podospicatin was methylated with dimethyl sulphate in acetone solution in the presence of anhydrous potassium carbonate. The trimethyl ether, after repeated crystallization from absolute ethanol, formed prisms, m.p. 160–162°.

(Found: C, 64·5; H, 5·4; OMe, 41·6; Calc. for $C_{20}H_{20}O_7$: C, 64·5; H, 5·4; 5 OMe, 41·7%.)

Ultra-violet spectrum: λ_{max} 253 mμ (log ε 3·33), 299 mμ (log ε 3·11).

Alkaline degradations of podospicatin trimethyl ether. A solution of the trimethyl ether (279 mg) in ethanolic potassium hydroxide (20%; 5 ml) was refluxed for 5 hr. After dilution with water (15 ml) and removal of ethanol *in vacuo*, saturation with carbon dioxide precipitated a gum which was removed with ether. Repeated crystallization of this material from aqueous ethanol gave colourless needles of the benzyl ketone (II), m.p. 102–104° (248 mg).

(Found: C, 63·3; H, 6·5; OMe, 40·5; Calc. for $C_{19}H_{22}O_7$: C, 63·0; H, 6·1; 5 OMe, 42·8%.)

Ultra-violet spectrum: λ_{max} 281 mμ (log ε 3·31), 3·22 mμ (log ε 3·07).

Steam distillation of the acidified aqueous mother liquors gave an acid distillate which readily reduced Tollens' reagent. After neutralization with sodium hydroxide (0·79 equivalent) an aqueous solution of S-benzylthiourea hydrochloride (150 mg), was added and the solution allowed to evaporate at room temp. The product, after crystallization from aqueous ethanol, had m.p. and mixed m.p. 146° with S-benzyl thiourea formate.

The benzyl ketone (II; 160 mg) was dissolved in water (0·25 ml) containing sodium hydroxide (1·5 g) and the solution heated to 220° for 45 min. The products of the fusion were divided into acid and phenolic fractions in the usual manner. The major acid component crystallized from water in rods, m.p. 120–121° (24 mg). (Found: C, 61·4; H, 6·0; $C_{10}H_{12}O_4$ requires: C, 61·2; H, 6·2%.) The melting point was not depressed by homogentisic acid dimethyl ether (m.p. 120–121°) prepared by ozonolysis of 2:5-dimethoxyallylbenzene.[7]

The major phenolic product from the alkaline fusion crystallized from benzene in plates, m.p. 148–149° (33 mg). (Found: C, 58·9; H, 6·6; OMe, 48·6; $C_9H_{12}O_4$ requires: C, 58·7; H, 6·6; 3 OMe, 50·5%.) Chapman, Perkin and Robinson[8] record m.p. 147° for antiarol (3:4:5-trimethoxyphenol).

Acknowledgements—Assistance is gratefully acknowledged from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, the Research Grants Committee of the University of New Zealand and by one of us (B. F. C.) for a University Research Fund Fellowship.

[6] A. G. Perkin, *J. Chem. Soc.* 2354 (1914).
[7] F. Mauthner, *J. Prakt. Chem.* **102**, 41 (1921).
[8] E. Chapman, A. G. Perkin and R. Robinson, *J. Chem. Soc.* 3028 (1927).

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VOL.
6
1959

CHEMISTRY OF THE PODOCARPACEAE—II

THE ISOLATION OF GENISTEIN FROM *PODOCARPUS SPICATUS* AND THE CONSTITUTION OF PODOSPICATIN

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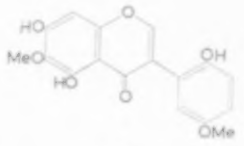
(*Received* 10 *November* 1958)

Abstract—Genistein has been isolated from the heartwood. Podospicatin has been shown to have the constitution 5:5′:7-trihydroxy-2′:-6-dimethoxy*iso*flavone.

IN a more systematic extraction of the heartwood of *Podocarpus spicatus* matairesinol and podospicatin have again been isolated and, in addition, the *iso*flavone genistein. Other constituents will be described in a further communication.

The remaining structural feature required for podospicatin[1] is the position of the two methoxyl groups. Since podospicatin gave no positive Bargellini test for three vicinal phenolic groups[2] at least one of the hydroxyl groups of the 3-phenyl component is unmethylated. Tests for *o*- or *p*-dihydroxyphenols with chloropentammino-cobaltic chloride[3] were also negative. On the basis of these colour tests podospicatin is either 5:5′:7-trihydroxy-2′:6-dimethoxy*iso*flavone or 2′:5:7-trihydroxy-5′:6-dimethoxy*iso*flavone. That the latter is correct was shown by degradation of the triethyl ether. Vigorous alkaline treatment of podospicatin triethyl ether gave a phenol and an acid. The same phenol, 3:5-diethoxy-4-methoxyphenol, would be expected from both possible formulations. The synthetic compound was shown to be identical with that obtained by degradation. The acid was shown to be 2-ethoxy-5-methoxyphenylacetic acid by comparison with a synthetic specimen. Podospicatin is, therefore, 2′:5:7-trihydroxy-5′:6-dimethoxy*iso*flavone(I).



I

Podospicatin 7-methyl and 2′:7-dimethyl ether were prepared by Simpson and Beton's method.[4]

In agreement with Swain[5] a marked shift in the ultra-violet absorption spectra of podospicatin, its 7-methyl and 2′:7-dimethyl ether, has been observed on the addition of aluminium chloride to the ethanolic solution.

[1] L. H. Briggs and B. F. Cain, *Tetrahedron* **6**, 143 (1959).
[2] G. Bargellini, *Gazzetta* **49**, 47 (1919).
[3] Y. Sashina, J. Asano and Y. Ueno, *Bull. Chem. Soc. Japan* **17**, 104 (1942).
[4] T. H. Simpson and J. L. Beton, *J. Chem. Soc.* 4065 (1954).
[5] T. Swain, *Chem. & Ind.* 1480 (1954).

EXPERIMENTAL

Microanalyses were carried out by Dr. A. R. Campbell, University of Otago. Ultra-violet spectra were measured in ethanol.

Extraction. Dry, finely ground heartwood of *Podocarpus spicatus* was successively extracted with light petroleum (b.p. 60–90°) and ether in a large Soxhlet extractor. Evaporation of the light petroleum extract to 1/25 volume precipitated a gum. After digestion with a little light petroleum this was crystallized from ethanol and repeatedly from acetic acid to give podospicatin, m.p. 213·5–214°.

Ultra-violet spectrum: λ_{max} in 0·1% ethanolic aluminium chloride solution, 275 mμ (log ε 4·34), 310 mμ (log ε 4·16).

Infra-red spectrum (KBr): 3390, 3175, 2941, 2817, 2597, 1656, 1634, 1567, 1499,1464, 1435, 1370, 1335, 1299, 1261, 1209, 1181, 1157, 1131, 1063, 1036, 991, 964, 932, 917, 856, 817, 803, 742, 718, 683 cm^{-1}.

The crystalline material, which formed after concentration of the ether extract to 1/10 volume, was repeatedly crystallized from 60% acetic acid to give rhombic crystals of matairesinol, m.p. and mixed m.p. 117–119°. Further concentration of the ether extract gave a gum which could be separated into podospicatin and matairesinol by fractional crystallization.

Acidic constituents were removed from the remaining ether extract by successive extraction with saturated sodium hydrogen carbonate, 10% sodium carbonate and 0·2% sodium hydroxide solutions followed by acidification. The material from the hydrogen carbonate extract is under investigation.

The material from the carbonate extract crystallized from 60% acetic acid to give matairesinol and a compound crystallizing in yellow needles, m.p. 293–294°. The latter has been identified with genistein, mixed m.p. 300–302° with an authentic specimen, m.p. 301–303°. (Found: C, 66·2; H, 3·7. $C_{15}H_{10}O_5$ requires: C, 66·8; H, 3·7%). The ultra-violet spectrum, λ_{max} 265 mμ (log ε 4·59) agrees with that, λ_{max} 263 mμ (log ε 4·57), recorded by Walter.[6] The melting points of the trimethyl ether, m.p. 164–165°, and the triacetate, m.p. 202–204°, agree with those reported by Seshadri[7] and Walz[8] respectively.

Alkaline fusion of podospicatin triethyl ether. A solution of podospicatin (1·485 g) in acetone was ethylated with diethyl sulphate in the presence of anhydrous potassium carbonate. The oily product was dissolved in ether, washed with sodium hydroxide solution and the solvent removed. The product (1·43 g) was mixed with sodium hydroxide (5 g) and water (2 ml) and heated to 220° for 50 min. The products were divided into acid and phenolic fractions in the usual way. The major phenolic compound crystallized from water in needles, m.p. 71–72°, (250 mg) raised to 83·5–84·5° on drying in a desiccator. (Found: C, 62·5; H, 7·3. $C_{11}H_{16}O_4$ requires: C, 62·3; H, 7·6%). The melting point was not depressed by a synthetic sample of 3:5-diethoxy-4-methoxyphenol[9] and the infra-red spectra of the respective samples were identical.

The major acid component from the alkaline fusion crystallized from water in plates, m.p. 103–104° (151 mg). (Found: C, 62·5; H, 6·6. $C_{11}H_{14}O_4$ requires: C, 62·8; H, 6·7%). The melting point was not depressed by a synthetic sample of 2-ethoxy-5-methoxyphenylacetic acid prepared by ozonolysis of 2-ethoxy-5-methoxyallylbenzene and the infra-red spectra of the respective samples were identical.

Infra-red spectrum (KBr): 3390, 3279, 2985, 2632, 2532, 1603, 1508, 1466, 1391, 1330, 1259, 1225, 1178, 1157, 1124, 1104, 1025, 994, 900, 861, 848, 814, 780, 743 cm^{-1}.

Synthesis of 2-ethoxy-5-methoxyphenylacetic acid. Quinol monomethyl ether (19 g) was allylated by refluxing with allyl bromide (24 ml) in acetone (500 ml) in the presence of anhydrous potassium carbonate (60 g) for 9 hr. The product from the acetone solution was taken up in ether and washed with sodium hydroxide solution and the solvent removed. The resultant liquid (22·5 g) failed to solidify and was submitted to Claisen rearrangement directly.

The allyl ether (22·5 g) and dimethylaniline (12 g) were refluxed for 45 min, dissolved in light petroleum and extracted successively with dilute sulphuric acid and 10% sodium hydroxide solution. The alkali soluble material, after acidification and extraction with ether, yielded 2-allyl-4-methoxyphenol as an oil, b.p. 190° (bath temp.)/8 mm (17·6 g).

The above phenol (17·5 g) was ethylated by refluxing with diethyl sulphate (18 ml) in acetone

[6] E. D. Walter, *J. Amer. Chem. Soc.* **63**, 3273 (1941).
[7] T. R. Seshadri, *Curr. Sci.* **22**, 263 (1953).
[8] E. Walz, *Liebigs Ann.* **489**, 118 (1931).
[9] T. R. Seshadri and M. Krishnamurti, *Proc. Indian Acad. Sci.* **39**, 144 (1954).

(200 ml) in the presence of anhydrous potassium carbonate (60 g) for 16 hr. The material from the acetone solution was taken up in ether and washed with sodium hydroxide solution and the solvent removed. 2-Ethoxy-5-methoxyallylbenzene was obtained as an oil, b.p. 174–178° (bath temp.)/5 mm.

The oil (700 mg) was finally ozonized in carbon tetrachloride (25 ml) and the ozonide decomposed and oxidized by solution in glacial acetic acid and treatment with a mixture of hydrogen peroxide (30%, 2·5 ml), sulphuric acid (0·1 ml) and water (5 ml) under reflux for 2 hr. The product was taken up in ether and the acidic material removed with sodium hydrogen carbonate solution. After acidification the material was repeatedly crystallized from water to give colourless plates of 2-ethoxy-5-methoxyphenylacetic acid, m.p. and mixed m.p. with the degradation acid, 101–102°. The infra-red spectra of the two acids were also identical.

Podospicatin 7-methyl ether. Podospicatin (554 mg) was methylated by refluxing with dimethyl sulphate (0·31 ml, 1·1 mole) in acetone (150 ml) in the presence of sodium hydrogen carbonate (10 g) for 21 hr, with continuous passage of carbon dioxide. The product crystallized from glacial acetic acid in pale yellow, rectangular plates, m.p. 206·5–207·5°. (Found: C, 62·8; H, 5·0; OMe, 27·0; Calc. for $C_{15}H_7O_4(OMe)_3$: C, 62·8; H, 4·7; 3 OMe, 27·0%).

Ultra-violet spectrum: (9·67 mg/l.): λ_{max} 265 mμ (log ε 4·33), 301 mμ (log ε 4·11). λ_{max} in 0·1% ethanolic aluminium chloride solution: 277 mμ (log ε 4·23), 307 mμ (log ε 4·05).

Infra-red spectrum (KBr): 3413, 3125, 2915, 2849, 1650, 1618, 1580, 1490, 1456, 1425, 1374, 1321, 1287, 1276, 1236, 1211, 1176, 1139, 1080, 1059, 1041, 1010, 976, 932, 877, 855, 826, 812, 761, 741, 719, 699 cm^{-1}.

The product was soluble in warm sodium carbonate solution and gave a green ferric chloride coloration.

Podospicatin 2′:7-dimethyl ether. A solution of podospicatin (173 mg), dimethyl sulphate (3·6 ml), ethanol (21 ml) and N-sodium carbonate solution (39 ml) was maintained at 20–21° for 20 min, diluted with water (100 ml) and acidified. After standing, the product crystallized from 60% acetic acid in pale yellow hexagonal plates, m.p. 120–121·5°. (Found: C, 63·25; H, 5·0; OMe, 30·8; Calc. for $C_{15}H_6O_3(OCH_3)_4$: C, 63·7; H, 5·1; 4 OMe, 34·6%).

Ultra-violet spectrum (78·3 mg/l.): λ_{max} 262 mμ (log ε 4·44), 300 mμ (log ε 4·25). λ_{max} in 0·1% ethanolic aluminium chloride solution, 275 mμ (log ε 4·53), 307 mμ (log ε 4·46).

Infra-red spectrum (KBr): 3546, 3257, 2967, 1650, 1623, 1580, 1497, 1458, 1357, 1299, 1232, 1215, 1179, 1142, 1079, 1060, 1040, 1018, 985, 943, 917, 861, 817, 803, 770, 739, 714, 699 cm^{-1}.

The product was soluble in sodium hydroxide solution and gave a green ferric chloride coloration.

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VOL. 6 1959

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REACTION MECHANISMS IN REDUCTIONS BY METAL–AMMONIA SOLUTIONS

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(*Received* 18 *November* 1958)

Abstract—The mechanism is discussed of the reduction of monobenzenoid compounds by means of metals and acohols in liquid ammonia. Contrary to claims in the literature[1] *iso*quinoline and dibenzothiophene are both readily reducible by this method.

RECENTLY[1] the mechanism of the metal–alcohol–liquid ammonia reductions of monobenzenoid compounds has been discussed in terms of the initial addition of a hydrogen atom, an hypothesis discussed by us in 1944[2] but shortly thereafter abandoned for what still appear sufficiently good reasons. We feel that a further critical consideration of the evidence is required in view of our belief that all of the phenomena can be correlated and explained on the basis of an initial stage of electron-addition.

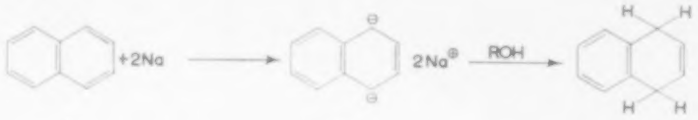
Initial stage of reduction

The first observation of crucial importance in this field was that of Wooster[3] who showed that the presence of alcohol in liquid ammonia permitted the reduction of benzene to occur, giving 1:4-dihydrobenzene, whereas in its absence there was no reaction. Wooster also provided some evidence that alkyl- or methoxy-benzenes are similarly reducible, but he did not analyse or examine the products in detail and wrongly guessed their formulae to be 1-substituted-1:4-dihydrobenzenes. They were later shown to be 1-substituted-2:5-dihydrobenzenes.[2]

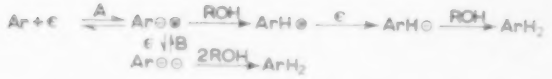
In the case of polycyclic compounds it was already known (e.g.[4]) that reduction could be experimentally carried out in two stages: an initial addition of metal electrons, to form an ionised salt, e.g. I → II, which by the action of a proton source (often in the working-up process) leads to a hydroderivative (e.g. III). We were impressed by the fact that if the processes are carried out under the correct experimental conditions the *same* product can be obtained from a two-stage process (when this is possible) and a one-stage process. We were reluctant, therefore, to postulate a new mechanism, such as hydrogen-atom addition, to account for the benzene reduction if a reasonable explanation could be found for the facts above. In lectures

[1] W. Hückel, B. Graf and D. Munkner, *Liebigs Ann.* **614**, 47 (1958). cf. W. Hückel and I. Nabik, *Ber.* **89**, 2115 (1956); W. Hückel and G. Graner, *Ber.* **90**, 2017 (1957).
[2] A. J. Birch, *J. Chem. Soc.* 430 (1944).
[3] C. B. Wooster, *U.S. Patent* 2182242 (1938).
[4] W. Hückel and H. Bretschneider, *Liebigs Ann.* **540**, 157 (1937).

over a number of years (e.g.[5]) we have advanced an explanation based on the following equilibria and reactions:



I II III



VOL. 6 1959

The important factors are the position of the equilibrium A, whether equilibrium B can be established at all and whether a sufficiently acid proton source (e.g. ROH) is present which can protonate the anion-radical. There is ample evidence for the reversibility of the electron-addition stage.[6] If the substance Ar contains only an isolated benzene ring, not carrying a carboxyl group, equilibrium A will be much further to the left than if Ar is polycyclic, when $Ar^{\otimes\ominus}$ will be much more stable. Addition of a second electron (equilibrium B) seems also very unlikely in a monobenzenoid system, although it is possible (e.g.[4]) with polycyclic compounds in the presence of a solvent such as ammonia, which is polar enough to stabilise the resulting ions by solvation. This solvation in fact explains the favourable influence of ammonia on the reduction processes in general.

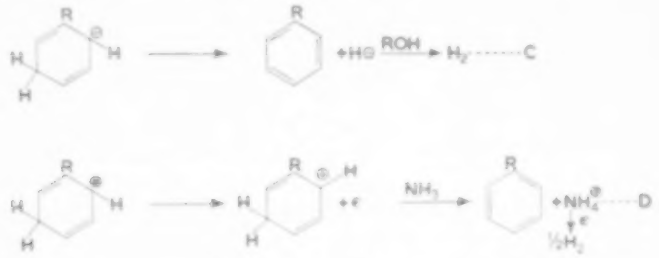
If the equilibrium A is produced at all with monobenzenoid substances then protonation of the anion-radical will permit reduction to proceed irreversibly. Ammonia apparently cannot provide the necessary proton because of its low acidity (pK about 34) but alcohols (pK about 16–18) can do so. This can be rationalised on the expected low basicity of the anion-radical, by analogy with ketyl radicals,[6] and is supported by the fact that even anions of type $ArH^{\ominus}$ have a basicity of the same order as $NH_2^{\ominus}$. With more highly acidic proton sources (the limit has not been defined) evolution of hydrogen gas occurs as a rapid competing reaction. The evolution of hydrogen gas from sodium and alcohols in ammonia is very slow.[7]

The first stages of the process are formally, but only formally, equivalent to the addition of a hydrogen atom. The distinction is important because on our mechanism it is possible to arrive at conclusions concerning relative rates and possible products by considering the nature and reactivity of the anion radical on the basis of the known electronic effects of substituents and of the ring system. For example, increasing difficulty of reduction can be correlated with increasing substitution by electron-repelling groups.[6]

We must briefly consider the evidence put forward by Hückel *et al.*[1] to support the hydrogen atom mechanism. The effect of finely divided transition metals in preventing reduction,[1] first observed with iron,[2] we have attributed to an acceleration of the slow reaction of alkali metal and alcohol in ammonia to give hydrogen gas; i.e. adsorbed hydrogen atoms are catalytically formed on the metal surface and combine to hydrogen molecules, thus rapidly removing the reducing agent. A possible

[5] A. J. Birch, *J. Roy. Inst. Chem.* 100 (1957).
[6] A. J. Birch, *Quart. Rev.* 69 (1950).
[7] A. J. Birch, *J. Chem. Soc.* 811 (1945).

practical explanation of the similar catalytic effects of aromatic compounds on hydrogen evolution may be the decomposition C below. In fact, potassium hydride is rapidly eliminated from the dihydroalkylbenzenes by the action of potassium amide in ammonia.[8] An alternative explanation is that in the ionising environment the protonated anion-radical may lose an electron to give the protonated hydrocarbon, a derivative of a strong acid which would immediately produce an ammonium cation (D). For experimental reasons not at present readily explicable, ammonium cations rapidly produce hydrogen gas with sodium in ammonia, and could well react with a very mobile electron before being neutralised by an anion.



Hückel *et al.*[1] also note differences in the behaviour on reduction at −50° of mixtures of alkylbenzenes compared with mixtures of naphthalene and alkylbenzenes. This they attribute to the naphthalene being reduced by initial electron addition while the monocyclic compounds are reduced by hydrogen atoms. Since these hydrocarbons at least partially crystallise and have a very low solubility in ammonia especially in the presence of ions, we feel that these results cannot be simply interpreted in mechanistic terms, depending as they must on complex phase relations and details of experimental procedure.

A more important discrepancy is the claim[1] that *iso*quinoline and dibenzothiophene are reducible in a two-stage process of metal addition followed by proton addition, but not by the one-stage process, in which they are said merely to catalyse the evolution of hydrogen gas. It must be noted that differing *products* by the two process are explicable (e.g.[6]) but since on our view the presence of alcohol assists the initial stage then reduction of some kind should occur in one stage if it occurs in two stages.

Under our usual experimental conditions (which are not those attributed to us by Hückel *et al.*[1] see below) we find that both of these substances are readily reducible.

In the case of quinoline the major product is 1:2:3:4-tetrahydroquinoline containing a trace of dihydroquinoline, as shown by the isolation of a very small proportion of the crystalline trimer, m.p. 187°, of the latter. Using two equivalents of sodium about half of the starting-material is unchanged. The production of the tetrahydro-derivative is not surprising. Either of the possible dihydro-derivatives reduced in the heterocyclic ring (IV) or (V) should more readily be reducible than the starting-material; the former is a styrene derivative, the latter contains $\diagdown C{=}N{-}\diagup$. Reduction in the heterocyclic ring is to be expected because of the higher electron-affinity of

[8] A. J. Birch, *J. Chem. Soc.* 1642 (1947).

nitrogen compared with carbon. The production of dihydro*iso*quinoline in absence of ethanol[1] is to be expected not because the initial step is different but because the anion (VI) should survive until the reaction is worked up since its negative charge will prevent further electron addition as noted in cases.[6,9]

IV

V

VI

VII

VIII

Hückel *et al.* probably failed to observe the reduction above since they were expecting a dihydro-derivative rather than the tetrahydro-derivative actually formed.

Dibenzothiophene is readily reducible, but requires six equivalents of sodium. The use of two equivalents[1] would therefore leave unchanged two-thirds of the starting-material; Hückel *et al.*[1] apparently missed the alkali-soluble product (VII). The position of the double bond in (VII) has not been definitely determined, except that it cannot be conjugated with the benzene ring. The initial thiol, convertible to a crystalline derivative by the action of sodium chloroacetate, cyclises on distillation to what must be a bridged-ring product such as (VIII). This can be oxidised to a crystalline sulphone, and cannot be dehydrogenated by sulphur to dibenzothiophene under conditions where the latter is fairly stable.

In connexion with experimental conditions it may be noted that the process attributed by Hückel *et al.*[1] to Wibaut and Haak[10] is in fact closely similar to our usual experimental procedure. We have not since 1944 used the process of addition of the substance in alcohol to the metal dissolved in ammonia. We dissolve the substance, with at least 10 per cent of ethanol (or methanol) in the ammonia with a co-solvent such as ether or tetrahydrofuran if necessary, and add the metal slowly The reason for this was clearly pointed out in 1946[11] and lies in the ability of the excess metal (or metal amide produced) to catalyse conjugation of double bonds which leads to further reduction. The very useful procedure of Wilds and Nelson[12] using initially excess lithium metal must partially owe its success to the lesser tendency of this metal or its derivative to produce such secondary reactions.

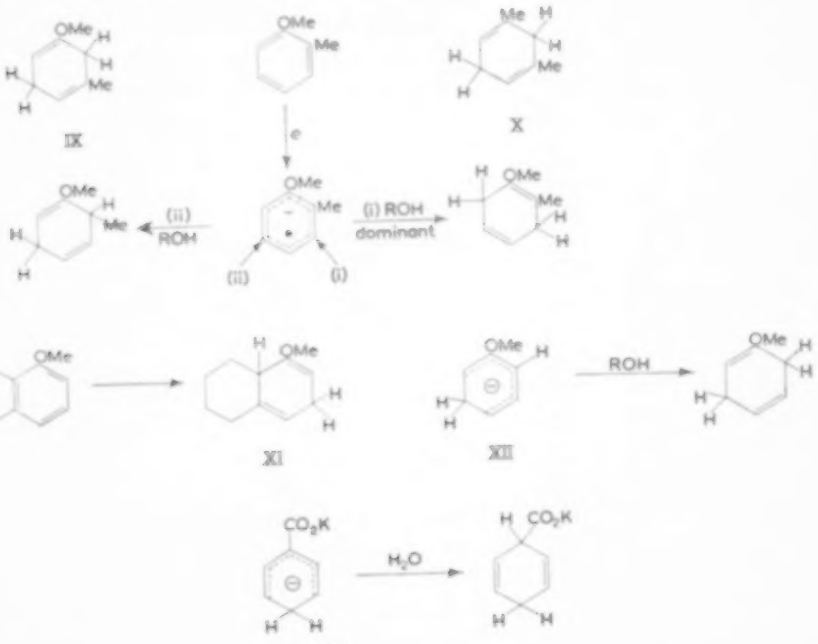
Structures of the products

The structures of the dihydrobenzenes will be determined by two factors which should be definable on the above mechanism. (i) The position of addition of the proton to the anion-radical $Ar\otimes\ominus$ and (ii) the position of addition of the second proton to the mesomeric anion $ArH\ominus$. The expectation would be that addition to the anion-radical should occur in the position of greatest *free* charge density, i.e. *meta*

[9] A. J. Birch, *J. Proc. Roy. Soc. N.S.W.* **83**, 245 (1950); A. J. Birch and H. Smith, *Quart. Rev.* **17** (1958).
[10] J. P. Wibaut and F. A. Haak, *Rec. Trav. Chem. Pays-Bas* **67**, 85 (1948).
[11] A. J. Birch, *J. Chem. Soc.* 595 (1946).
[12] A. L. Wilds and H. A. Nelson, *J. Amer. Chem. Soc.* **57**, 5360 (1953).

to an *o*, *p*-directing substituent, since accumulation of charge in the *ortho* and *para* positions will be opposed by the substituent. Similarly, addition might be expected *para* to a *m*-directing group, but in practice carboxyl is the only group of this type which is not itself reduced before the ring. In this case in fact the 1:4-dihydrobenzoic acid finally results.[13]

With two or more substituents, on the same grounds, we would expect addition: (i) *meta* to the most strongly *o*- *p*-directing group; and (ii) for preference not in a position occupied by an *o*- *p*-directing group. With *meta*- or *para*- dialkyl- or methoxy-alkyl- etc. benzenes the results agree quite simply with expectations,[6] the products being 2:5-dihydro-derivatives, e.g. *m*-tolyl methyl ether → (IX);[2] *m*-xylene → (X)[2]. Benzenes with *ortho* substituents involve a further complication. Experimentally, addition occurs *ortho* rather than *para* to a substituent, for example 1-methoxy-2-methyl benzene gives a mixture of the 2:5- and 3:6-dihydroderivatives, in which the latter predominates.[2] 5-Methoxy-1:2:3:4-tetrahydronaphthalene appears to give only one product (XI)[2] in accord with the rule.



This rule can presumably be correlated with the usual greater effect of an alkyl group in the *para* rather than the *ortho* position; it is also observed in cases of ether fissions with metal–ammonia solutions.[6]

The position of addition of the second proton has already been considered in detail[13] and it has shown experimentally that anions of types (XII) or (XIII) do lead on irreversible protonation to unconjugated dihydrobenzenes identical with those produced by direct reduction of the corresponding aromatic compounds. Such mesomeric anions are therefore likely intermediates in the reduction, as already

[13] A. J. Birch, *J. Chem. Soc.* 1551 (1950).

postulated. Hückel *et al.*[1] apparently do not disagree with our views on these later stages.

We feel that the problem of the initial stage is not yet settled, but that our approach can at present explain all the known facts, and that it provides a more logical basis for correlations and a better aid to finding appropriate experimental conditions.

EXPERIMENTAL

Reduction of isoquinoline

(a). To a solution of *iso*quinoline (12·5 g) in liquid ammonia (300 cc) and ethanol (45 cc) was added sodium (5 g, 2·25 atoms) in small pieces over 5 mins. After evaporation of the ammonia, water was added and the product worked up as usual to give a yellow oil (11·8 g) b.p.121–122°/10 mm; n_D^{22} 1·1578. The ultra-violet absorption curve was nearly identical with that of a mixture of equal parts of *iso*quinoline and 1:2:3:4-tetrahydro*iso*quinoline. The components were separated by passing moist carbon dioxide into an ethereal solution to precipitate the carbonate of the tetrahydro-compound. The weight of carbonate produced also supports the equal ratio of products. Tetrahydro*iso*quinoline was characterised as the picrate m.p.199–200° and hydrochloride m.p.198°, and *iso*quinoline as the picrate m.p. 223°. Several cc of the product kept after addition of a few drops of methanol deposited a few mg of crystals m.p.187° which may be one of the trimers of dihydro*iso*-quinoline (cf.[1]); the original material therefore probably contains a very small proportion of dihydro-derivative.

(b). A solution of *iso*quinoline (12·5 g) in liquid ammonia (450 cc) and ethanol (70 cc) was reduced with sodium (10 g, 4·5 atoms). Worked up as before, the product was 1:2:3:4-tetrahydro-*iso*quinoline as an almost colourless oil (11·5 g) b.p.118–120°/10 mm. The picrate had m.p. 199–200° (Found: C, 50·1; H, 3·7; N, 15·25; Calc, for $C_9H_{11}N$, $C_9H_9O_7N_3$: C, 49·7; H, 3·9; N, 15·5%). The hydrochloride had m.p. 198° (Found: C, 63·25; H, 7·5; N, 8·15; Calc, for $C_9H_{11}N$, HCl: C, 63·7; H, 7·1; N, 8·3%). The ultra-violet spectrum of the base in ethanol had λ_{max} 266 mμ, ε 410; λ_{max} 273 mμ, ε 410, and λ_{min} 240 mμ.

Reduction of dibenzothiophene

(a). Dibenzothiophene (6 g) in dry ether (120 cc) was added to liquid ammonia (350 cc) and ethanol (35 cc). Sodium (2·2 g, 3 atoms) was then introduced and the product worked up as usual but in an atmosphere of nitrogen. The ethereal extract gave unchanged dibenzothiophene (3·1 g) m.p. 96–97° in an almost pure state. The alkaline solution was acidified and extracted with ether. The resulting oil did not crystallise, but after warming with sodium chloroacetate in alkaline solution under nitrogen gave rise to 2 (cyclo*hex-2′-enyl*) *phenylthiol carboxymethyl ether* from light petroleum (b.p. 40–60°) m.p. 96–98° (Found: C, 68·00 H, 6·45; S, 12·3; Equiv. 248 $C_{14}H_{16}O_2S$ requires C, 67·7; H, 6·45; S, 12·9%, Equiv. 248). Distillation of the reduction product gave an oil (2·8 g) b.p. 100°/0·2 mm n_D^{22} 1·6050 (Found: C, 75·9; H, 7·3; S, 17·2 $C_{12}H_{14}S$ requires C, 75·8; H, 7·4; S, 16·8%), possibly 3:4-*benz*-2-*thia*(1:3:3)*bi*cyclo*nonene* (VIII). It no longer dissolved in alkali and gave no nitroprusside test. The ultra-violet absorption had λ_{max} 250 mμ, ε 8900 and λ_{max} 288 mμ, ε 1500. It gave no picrate, and an attempt to dehydrogenate it with sulphur at 200° failed to yield dibenzothiophene. Oxidation of the substance (0·5 g) was carried out in acetic acid (5 cc) with hydrogen peroxide (5 cc 30%) at reflux for 30–40 mins. The product, was diluted with water, extracted with ether and the viscous oil crystallised from ethyl acetate-light petroleum (b.p. 40–60°). The *sulphone* crystallised in plates m.p. 75–76·5° (Found: C, 64·4; H, 6·2; S, 13·1; $C_{12}H_{14}O_2S$ requires C, 64·9; H, 6·3; S, 14·4%).

It was found that by increasing the proportion of sodium in the original reduction to 6·5 atoms the yield of alkali-soluble product was 85%. The substance so obtained was warmed in alkaline solution with excess methyl sulphate. The resulting alkali-insoluble oil, b.p. 110°/0·2 mm is presumably 2(cyclo*hex-2′-enyl*)*phenylthiol methylether*. Found: C, 76·1; H, 7·95; S, 15·4. $C_{13}H_{16}S$ requires C, 76·45; H, 7·9; S, 15·65; λ_{max} 253 mμ, ε 7720. (cf. the absorption of *cyclo*hexylphenyl sulphide[14] λ_{max} 258·5 mμ, ε, 7000).

Acknowledgement—We are indebted to the Colombo Plan for a Fellowship (D. N.).

[14] H. P. Koch, *J. Chem. Soc.* 391 (1949).

Tetrahedron, 1959, Vol. 6, pp. 154–160. Pergamon Press Ltd. Printed in Northern Ireland

GEWINNUNG UND EIGENSCHAFTEN EINIGER TITANORGANISCHER VERBINDUNGEN

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Zusammenfassung—Durch die Zusammenwirkung des Titan-tetrachlorids mit den Alkonolen wurde eine Reihe von titanorganischen Verbindungen wie $TiCl_3OR$ gewonnen,

(wo R = *iso*$C_3H_7^-$; *sed* $C_4H_9^-$; *cyclo*C_6H_{11}; *tert* C_4H_9)

Es ist dabei festgestellt worden, das die Verbindungen wo R das *secund.* oder *tert.* Radikal ist, im Gegensatz zu denen mit *primären* Radikalen, sich als unstabielen erweisen Während der Aufbewahrung bei Zimmertemperatur unterliegen sie einer schnelleren, bei 0° etwas langerer Zersetzung unter Bildung HCl, des Olefines und Halogen-alkylen. Den festen Rückstand bildet Titan-chloroxyd, das einen wirksamen Katalysator für Propylen, *iso*Butylen und Styrol–Polymerisation darstellt, wobei den Polymerisationsprozess Bildung der niedermolekularen Produkte begleitet. Das erwähnte Titanchloroxyd gilt als ebenso aktiver katalysator beim Olefin–Hydrochlorieren.

Abstract—The action of $TiCl_4$ on alcohols gives compounds of the type $Ti(OR)Cl_3$ where R = *iso*$C_3H_7^-$, *sec.*$C_4H_9^-$, *tert.*$C_4H_9^-$ and *cyclo*$C_6H_{11}^-$. Compounds where R is a *secondary* or *tertiary* group as distinct from a *primary* group are unstable, decomposing on keeping at room temperature and slowly at 0° yielding HCl, an olefine and alkyl halide and a residue of titanium oxychloride. The latter is a very active catalyst for the polymerisation of propylene *iso*butylene and styrene forming polymers of low molecular weight. Titanium oxychloride is also an active catalyst in the addition of HCl to olefines.

NACH den hervorragenden Entdeckungen von Ziegler und Natta über die Olefine–Polymerisation erwecken titanorganische Verbindungen grosses Interesse als eventuelle Zwischenprodukte im Reaktionsablauf zwischen Trialkylaluminium und $TiCl_4$. Die chemische Literatur verfügt über die Angaben von der Gewinnung etlicher wirksamer katalytischer Systeme für die Olefine–Polymerisation, die titanorganische Verbingungen enthalten.[1,2]

Von besonderem Interesse war auch eine nähere Bekanntschaft mit den titanorganischen Verbindungen, vom Standpunkte ihrer Aktivität in der Olefine–Polymerisation betrachtet. Die Untersuchung verschiedener titanorganische Verbindungen enthaltender katalytischer Systeme hat ergeben, dass das System $Ti(OC_3H_7^{iso})_4 + TiCl_4$ ein aktiver Katalysator der Propylen–Polymerisation mit Entstehung eines flüssigen Polymers ist. Die Ausbeute an Polymer war von dem Molarverhältnis zwischen Komponenten des Katalysators stark beeinflusst. (Abb. 1). Da beim Molarverhältnis $TiCl_4 : Ti(OC_3H_7^{iso})_4 = 1 : 2.5$ gar keine Polymerisation stattgefunden hat, beim Verhältnis 3 : 6 aber die Polymerausbeute 93–96% betrug, war es anzunehmen, dass in diesem Falle als Polymerisationskatalysator eine Verbindung der $TiCl_3OR$–Art auftritt, die durch Radikalenumsetzung nach Gleichung $3\ TiCl_4 + Ti(OR)_4 = 4\ TiCl_3OR$ gewonnen wird, was sonst beim Überschuss an $TiCl_4$ erfolgt.[3]

[1] G. Natta, P. Pino, G. Mazzanti und P. Longi, *Gazz. Chim Ital.* **87**, 570 (1957).
[2] G. Natta und P. Pino, *J. Amer. Chem. Soc.* **79**, 2957 (1957).
[3] A. N. Nesmeyanov, E. M. Brainina und R. H. Freidlina, *Ber. Akad. Wiss., U.S.S.R.*, **94**, 249 (1954).

Die Verbindungen $TiCl_3OC_2H_5$ (Schmp 81–82°), $TiCl_3OC_4H_9^{iso}$ (Schmp 82–83°) und $TiCl_3OC_3H_7^{n}$ (Schmp 66–67°), synthetisiert nach dem in der literatur angegebenen Verfahren[4] ohne und mit $TiCl_4$-Zusatz haben praktisch keine Propylen-Polymerisation hervorgerufen.

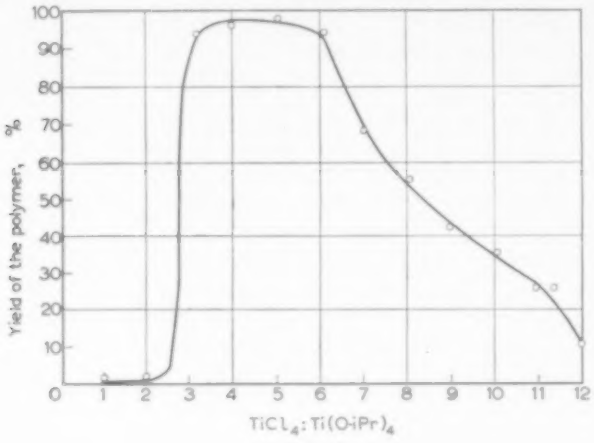


Abb. 1.

Das durch die Reaktion zwischen $TiCl_4$ und $Ti(OC_3H_7^{iso})_4$[5] ausgeschiedene Trichlor-Titan*iso*propylat polymerisierte intensiv das Propylen bis zum flüssigen Polymer.

Laut der Analyse war diese Verbindung keine absolut reine und enthielt geringere Mengen der unschmelzbaren, in organischen Lösungsmitteln unlöslichen Beimischung.

Unser Versuch,—das reine Präparat durch Vakuum-Sublimation oder Umkristallisation zu erhalten—blieb erfolglos wegen unvermeidlicher Produktzersetzung.

Die etwas geäuderte Methodik für die Synthese der $TiCl_3OR$-Verbindungen aus entsprechendem Alkohol und $TiCl_4$ Überschuss[4] erlaubte, das Trichlor-Titan*iso*-propylat als Reinprodukt zu erhalten. Das frisch präparierte, zusatzfreie $TiCl_3OC_3H_7^{iso}$ zeichnete sich in der Propylen-Polymerisation durch ungenügende Aktivität aus, die jedoch bei Verwendung einer geschlossenen Ampulle bedeutend erhöht wurde.

Es wurde konstatiert, dass $TiCl_3OC_3H_7^{iso}$ im Gegensatz zu den Verbindungen mit *primären* Radikalen keine stabiele Verbindung ist; Bei Aufbewahren zerfällt unter Ausscheidung gasförmiger Produkte und Bildung einer unschmelzbaren Verbindung.

Um den Mechanismus dieses Prozesses zu fassen, wurde das frisch präparierte, reine Produkt bei 45–50° im Laufe von 15–20 Std zersetzt und die Zersetzungsprodukte quantitativer sowie qualitativer Analyse unterworfen. Identifiziert waren folgende Verbindungen: Chlorwasserstoff, *iso*Propylchlorid, Titanchloroxyd und das an der Produktoberfläche gut absorbierte Propylen-Polymer. Das Polymerauscheiden erfolgte durch Zersetzung des Titanchloroxydes mit Wasser.

Das ähnliche Verfahren wurde auch für die Herstellung sonstiger titanorganischer

[4] A. N. Nesmeyanov, R. H. Freidlina und O. W. Nogina, *Akad. Wiss., U.S.S.R.* (Abt. *Chem. Wiss.*) 1037 (1952).
[5] D. Bradley, H. Hancock und W. Wardlaw, *J. Chem. Soc.* 2273 (1952).

Verbindungen benutzt und zwar: Derivaten der *secund* Alkohole–$TiCl_3OC_4H_9^{sec}$, $TiCl_3C_6H_{11}^{cyclo}$—die Literatur verfügt hier noch über keine Angaben, Diese Verbindungen waren noch weniger beständig als $TiCl_3OC_3H_7^{iso}$ und neigten zu rasherer Zersetzung bei der Aufbewahrung,

Es ist gezeigt, dass Zerfall der Produkte, durchgeführt in ähnlichen Bedingungen mit auschliessender Destillation der flüssigen Abscheidungsprodukte, denselben Reaktionsmechanismus besitzt. Bei $TiCl_3OC_4H_9^{sec}$–Zersetzung gewinnt man: HCl, *sec*-C_4H_9Cl, Titanchlorxyd, Butylen–Polymer. In dem Falle mit $TiCl_3OC_6H_{11}^{cyclo}$ dementsprechend: HCl. *cyclo*-$C_6H_{11}Cl$, Titanchloroxyd und Spuren des *cyclo*-Hexankondensation–produktes.

Die Zersetzungsbilanz für alle oben erwähnten titanorganischen Verbindungen ist in der Tabelle I niedergelegt. Der etwas zu niedrige Chlor—Gehalt in Titanchloroxyd und unvollkommenes Gleichgewicht in Cl und Ti beim $C_6H_{11}OTiCl_3$—Zerfall lassen sich durch partielle Titanchloroxyd–Zersetzung erklären, die beim Entfernen flüssiger Produkte unter Vakuum stattfand; das dabei abgetrennte $TiCl_4$ wurde mit *cyclo*-Hexylchlorid fortgetragen. Der Cl und Ti Gehalt, bestimmt im Wasser nach dem Abwaschen von *cyclo*-$C_6H_{11}Cl$, entsprach den in der Bilanz fehlenden Mengen. Partielle Zersetzung dieser Verbindungen wurde von gleichzeitiger.

TABELLE 1. BILANZTABELLE FÜR ZERSETZUNG VON $TiCl_3OR$ (WO R—$C_3H_7^{iso}$, $C_4H_9^{sec}$, $C_6H_{11}^{cyclo}$).

Gewog. Substanz g	Zersetzungsprodukte							
	Titancloroxyd		HCl		RCl		Polymerisations-produkt	
	g	%	g	%	g	%	g	%
1. 29,54	19,78	67,00	1,85	6,27	6,14	20,80	1,40	4,75
22,13	14,98	67,69	0,96	4,33	5,36	24,24	0,81	3,66
24,55	16,25	66,30	1,75	7,14	4,98	20,35	1,15	4,68
2. 14,10	9,68	68,65	0,84	5,96	1,87	13,35	1,47	10,44
15,20	8,76	57,65	1,13	7,44	3,83	25,20	1,39	9,15
3. 11,82	4,88	41,32	0,84	7,10	4,17	35,27	0,22	1,87
23,60	10,00	42,45	0,64	2,71	11,24	47,66	0,13	0,56
24,13	12,45	51,65	1,70	7,05	9,40	38,80	0,20	0,83

1. $TiCl_3OC_3H_7^{iso}$; 2. $TiCl_3OC_4H_9^{sec}$; 3. $TiCl_3OC_6H_{11}^{cyclo}$

Synthese derselben begleitet unter Entwicklung geringerer Titanchloroxyd–Mengen. Beim Versuch, $TiCl_3OC_4H_9^{tert}$ ähnlich zu synthesieren, erfolgte unverzügliche Zersetzung des Stoffes zusammen mit seiner Bildung. In Ergebnis war nur Titanchloroxyd ausgeschieden mit *iso*Butylen–Polymer, adsorbiert auf seiner Oberfläche. Nach dem Abtreiben des festen Produktes waren in der Lösung *tert* Butylchlorid und zusätzliche Menge vom *iso*Butylen–Polymer.

Titanchloroxyd,* erhalten durch Zersetzung der Verbindungen wie $TiCl_3OR$ wo R—das *secund* oder *tert* Radikal, liess sich als wirksamer Katalysator der Propylen-Polymerisation erklären. Die dabei erzielten Ergebnisse sind in der Tabelle II angeführt.

Die Polymerisation mit genannten Titanverbindungen als Katalysatoren verlief unter ziemlich milderen Bedingungen: Temp. 90–100°, Reaktionsdauer 3–4 Std.

TABELLE 2. PROPYLEN-POLYMERISATION MIT KATALYSATOREN $TiCl_3OR$ (WO OR—DER REST EINES *sekund* ODER *tert*. ALKOHOLS IST) UND IHREN ZERSETZUNGSPRODUKTEN POLYMERISATIONSBEDINGUNGEN: t = 90–100° DAUER 3–4 STD

(No.)	Katalysator	Aufbewahrungszeit Tagen	Menge, g	C_3H_6 g	Polymer-Ausbeute	
					g	%
1	2	3	4	5	6	7
1.	$TiCl_3OC_3H_7^{iso}$ [a]	frisch präpar	0,30	2,47	2,34	95,0
2.	$TiCl_3OC_3H_7^{iso}$ [a]	frisch präpar	0,25	2,71	2,33	86,0
3.	$TiCl_3OC_3H_7^{iso}$ [b]	frisch präpar	0,25	2,55	0,35	13,5
4.	$TiCl_3OC_3H_7^{iso}$ [b]	frisch präpar	0,27	2,66	0,72	27,0
5.	$TiCl_3OC_3H_7^{iso}$ [b]	1	0,25	2,54	1,58	62,2
6.	$TiCl_3OC_3H_7^{iso}$ [b]	2	0,23	2,22	1,54	69,5
7.	$TiCl_3OC_3H_7^{iso}$ [b]	3	0,25	2,30	1,93	84,0
8.	$TiCl_3OC_3H_7^{iso}$ [b]	4	0,23	2,41	2,26	94,0
9.	$TiCl_3OC_3H_7^{iso}$ [b]	6	0,24	2,48	2,39	96,4
10.	Titanchloroxyd [c]		0,29	2,21	2,21	96,7
11.	Titanchloroxyd [d]		0,25	2,08	1,96	94,3
12.	$TiCl_3OC_4H_7^{sec}$	frisch präpar	0,31	2,87	1,66	57,8
13.	$TiCl_3OC_4H_7^{sec}$	frisch präpar	0,28	2,90	0,69	23,8
14.	$TiCl_3OC_4H_7^{sec}$	2	0,28	2,86	2,51	87,8
15.	$TiCl_3OC_4H_7^{sec}$	3	0,27	2,65	2,52	96,2
16.	Titanchloroxyd [e]		0,25	2,14	1,76	82,4
17.	Titanchloroxyd [f]		0,26	2,75	2,70	98,2
18.	$TiCl_3OC_6H_{11}$	frisch präpar	0,27	2,91	1,14	39,2
19.	$TiCl_3OC_6H_{11}$	frisch präpar	0,30	2,14	1,13	62,2
20.	$TiCl_3OC_6H_{11}$	1	0,26	2,54	1,05	41,4
21.	$TiCl_3OC_6H_{11}$	2	0,27	2,62	1,06	40,5
22.	Titanchloroxyd [g]		0,27	2,53	2,03	80,2
23.	Titanchloroxyd		0,25	2,20	1,88	85,5
24.	Titanchloroxyd		0,25	2,35	2,26	96,1
25.	Titanchloroxyd		0,26	2,55	2,48	96,8

[a] erhalten durch Radikalen-Umtauschreaktion aus $TiCl_4$ und $Ti(OC_3H_7^{iso})_4$.
[b] Rein, ohne Beimischungen
[c] erhalten durch Zersetzung $TiCl_3OC_3H_7^{iso}$
[d] ausgeschieden bei Synthese $TiCl_3OC_3H_7^{iso}$
[e] erhalten durch Zersetzung $TiCl_3OC_4H_7^{sec}$
[f] ausgeschieden bei Synthese $TiCl_3OC_4H^{sec}$
[g] erhalten durch Zersetzung $TiCl_3OC_6H_{11}^{cyclo}$
[h] ausgeschieden bei Synthese $TiCl_3OC_6H_{11}^{cyclo}$
[i] ausgeschieden bei Synthese $TiCl_3OC_4H_9^{terz}$

* Titanchloroxyd, erhalten durch partielle Hydrolyse mit Wasser von $TiCl_4$, erwies sich als wenig ktiv für die Propylen-Polymerisation.

Das dabei gewonnene Polypropylen war eine farblose, olärtige Flüssigkeit, aus dem Gemisch ungesättigter Kohlenwasserstoffe bestehend. Die Ergebnisse vom Abdestillieren und von der Analyse je nach Fraktion sind in der Tabelle III angeführt.

Diese Katalysatoren bedingen auch intensive Polymerisation des *iso*Butylens und Styrols, die bei niedrigeren Temperaturen unter Entwicklung flüssiger und halbfester Polymere erfalgt. Die anderen von den untersuchten Monomere Vinylchlorid,

TABELLE 3. ABDESTILLIEREN UND ANALYSE DER POLYPROPYLEN-FRAKTIONEN

Fr. No.	Siedepunkt °C/mm Hg	g	%	n_d^{20}	d_4^{20}	M	Brom-zahl $\frac{g\ Br_2}{100_g}$	Abspaltungs-zahl* $\frac{g\ Br_2}{100_g\ Prod}$
1.	37–49/760	13,05	8,66	1,3758		86,0	19,4	0
2.	67–85/760	9,52	6,32	1,3978	0,7003	107,0	87,8	40,1
3.	96–127/760	12,40	8,24	1,4104	0,7432	121,1	115,3	36,5
4.	128–136/760	15,37	10,20	1,4195	0,7651	130,5	127,0	62,2
5.	137–145/760	3,34	2,22	1,4220	0,7903	133,4	125,6	64,8
6.	62–100/30	40,50	26,90	1,4450	0,7949	175,0	98,5	62,0
7.	74–90/10	20,34	13,50	1,4550	0,8110	191,5	90,3	52,1
8.	110–150/13	25,60	17,00	1,4703	0,8501	220,3	60,8	44,3
9.	Ruckstand	10,50	6,96	1,4770	0,9219	428,0	17,0	10,5
10.	Ges.	150,62	100					

* Die Abspaltungszahl bezeichnet den Verzweigungsgrad eines Kohlenwasserstoffes, wurde nach Galpern-Verfahren berechnet.[6]

Metylmetakrylat, Butylmetakrylat und Nitrylakrylsäuere erwiesen keine Tendenz zur Polymerisation.

An Hand der Produkte, erhalten bei der Zersetzung der Verbindungen $TiCl_3OR$, wo R—das *secund* oder *tert* Radikal ist, darf angenommen werden, dass die primären Prozesse sind:

$$TiCl_3OC_nH_{2n+1} \rightarrow TiOCl_2 + C_nH_{2n} + HCl \quad (1)$$

$$TiCl_3OC_nH_{2n+1} \rightarrow TiOCl_2 + C_nH_{2n+1}Cl \quad (2)$$

Im Falle (1) sollen als *secund* Reaktionen erscheinen:

$$C_nH_{2n} + HCl \rightarrow C_nH_{2n+1}Cl \quad (3)$$

$$mC_nH_{2n} \rightarrow (C_nH_{2n})_m \quad (4)$$

Im Falle (2)—die Zersetzungsreaktion für das entstehende Alkylchlorid:

$$C_nH_{2n+1}Cl \rightarrow C_nH_{2n} + HCl \quad (5)$$

mit auschliessender Olefine–Polymerisation nach (4).

Für die genauere Bestimmung des Zerfallmechanismus in den Reaktionen: Olefine–Hydrochlorieren und Alkylchloride–Dehydrochlorieren wurde die Aktivität des bei der Zersetzung entstandenen Titanchloroxydes untersucht. Es hat sich

[6] G. D. Ga'pern, Vorträge des Erdölforschungsinstitutes Akad. der Wissensch. der UrSSR. B. 5, 1954, s. 141.

herausgestellt, dass Titanchloroxyd ein wirksamer Katalysator im Olefine–Hydrochlorieren ist. Beim Durchlassen von Propylen, *iso*Butylen, *cyclo*Hexen. gemischt mit Chlorwasserstoff bei der Temperatur 60–65° durch die Katalysator–Schicht wurden entsprehende Alkylchloride mit guter Ausbeute gewonnen.

Es trat keine Zersetzung der Alkylchloride in Olefin und Chlorwasserstoff mit dem genannten Katalysator ein. Es wird also angenommen, dass die Zersetzung der $TiCl_3OR$–Verbindungen, wo R—ein Rest des *secund* oder *tert* Alkohols ist, nach Gleichung (1) mit nachfolgenden, parallel ablaufenden Reaktionen (3), (4) verläuft. Die Ausbeute an Polymer und Alkylchlorid ist dabei von der Natur des zu erhaltenden Olefin abhänging (siehe Tabelle 1).

Das beschriebene Titanchloroxyd wirkt auch in Anwesenheit vom $Al(C_2H_5)_3$ als aktiver Katalysator der Propylen–Polymerisation unter Entwircklung einer hochmolekularen Polymerverbindungen und zwar des Polypropylens,

EXPERIMENTALER TEIL

$TiCl_3OC_3H_7^{iso}$—*Gewinnung*. In einen Kolben (Kolben mit Doppelhals; versehen mit Rückkuhler und Tropftrichter; die letzten—von der Luftfeuchtigkeit durch $CaCl_2$—Röhre geschützt.) wurde 71,3 g (0,37 Mol) $TiCl_4$ in 150 cc absol Petroläther (Sdp 60–70°) eingesetzt und während 1 Std die Lösung von 15 g (0,25 Mol) des sorgfältig getrockneten *iso*Propyl-Alkohols in 100 cc Petroläther unter Eiskühlung zugetropft. Nach dem Stehenlassen bei der Raumtemperatur (1 Std) wurde das Reaktionsgemisch bis zum leichten Sieden des Lösungemittels (3 Std) erhitzt; über Nacht bei Raumtemperatur hinterlassen. Der bei Synthese ausgefallene Rückstand wurde filtriert, ca 2/3 der ganzen Petrol-äther-Menge aus dem Filtrat abgetrennt. Aus der restlichen Lösung fielen unter Eiskühlung hellgelbe Kristalle in Tablettenform.

$TiCl_3OC_3H_7^{iso}$ Ausbeute 70–75%; Schmp 78–79°; (Ber. für $TiCl_3OC_3H_7^{iso}$: Ti, 22, 45; Cl, 49,9; $OC_3H_7^{iso}$, 27, 65. Gef. Ti. 22,5; Cl, 49,8; $OC_3H_7^{iso}$, 27,5%).

$TiClOC_4H_9^{sec}$ und $TiCl_3OC_6H_{11}$ (*cyclo*Hexyl) wurden nach ähnlicher Methode erhalten, mit Ausnahme davon, dass der Petroläther hier unter Vakuum dei 25–30° abgetrennt wurde zwecks Herabsetzung des Produktzerfalls.

$TiCl_3OC_4H_9^{sec}$ hellgelbe Tabl; Ausbeute 52–56%; Schmp 54–56° (Ber. für $TiCl_3OC_4H_9^{sec}$; Ti, 21,05°, Cl, 46,85; $OC_4H_9^{sec}$, 32,0; Gef. Ti, 21,03; Cl, 46,5; $OC_4H_9^{sec}$ 32,0%). $TiCl_3OC_6H_{11}^{cyclo}$ kleinere hellgelbe Tabl; Ausbeute 41–43%; Schmp 75–76%; (Ber. für $TiCl_3OC_6H_{11}^{cyclo}$; Ti, 18, 19; Cl, 42°; Gef; Ti, 18,4; Cl, 42,8%).

Zersetzung der frisch präparierten titanorganischen Verbindungen. Eine Ampulle wird mit gewogener Substanzmenge gefüllt und den vorläufig gewogenen Schlangenempfanger (im Dewar Gefäss unterbracht; Kohlensäure und Azeton als Kuhlmittel) und U-Rohr (Geschützt von Luftfeuchtigkeit durch $CaCl_2$—Rohr. Inhalt v. U-Rohr: festes Ätznatron), angeschlossen. Die Ampulle wurde 15–20 Std im Wasserbad auf 45–50° erhitzt bis zum endgültigen. Verschwinden des Ausscheidens gasförmiger Produkte. Im Falle Ti $Cl_3OC_4H_9^{sec}$ und $TiCl_3OC_6H_{11}^{cyclo}$ wurde das Ausscheiden flüssiger Produkte (*sec* C_4H_8Cl und *cyclo*-$C_6H_{11}Cl$) unter Vakuum 100–150 mm Hg. ausgeführt.

Die bei der Zersetzung erhaltene HCl-Menge wurde nach Gewichtzunahme des U-Rohres mit NaOH ausgerechnet.

Das flüssige Kondensat nach dem Schlangenempfänger wurde gewogen und fraktioniert, die Fraktionen der Analyse unterworfen. Zur Analyse der frisch präparierten titanorgahischen Verbindung un des Titanchloroxydes (als Zerfallproduktes) wurde die gewogene Substanzmenge mit Wasser zersetzt; in der Wasserlösung bestimmte man:

1. Titan-Gehalt durch Gewichtsmethode als TiO_2
2. Chlor–Gehalt—merkurometrisch
3. Alkoxylgruppen-Gehalt (*iso*-C_3H_7O und *sec* C_4H_9O) durch Oxydation bis auf Keten mit 1 M-Lösung $K_2Cr_2O_7$ im H_2SO_4 Medium.[7]

Bei der Zersetzung $TiCl_3OC_3H_7^{iso}$ wurden folgende Verbindungen identifiziert: *HCl*. *iso*Propyl Chlorid Sdp 34,5–35°; $n_D^{15} = 1{,}3810$; lit. sdp 34,8°; $n_D^{15} = 1{,}3811$ (Ber. für *iso*C_3H_7Cl: Cl, 45,2;

[7] Berl–Lunge, Chemisch—technische untersuchungsmethoden, B. 3, T. 2, 1941, s. 253. russ. Auflage.

Gef: Cl, 44,9% und *Titanchloroxyd*, Ti, 30–31%; Cl, 46,5–47%; *iso*C_4H_7O, 3–5%; Propylen–Polymer, 4–7% mit Angaben: (Gef: C, 85,61; H, 13,80% Ber. für *n* C_3H_6: C, 85,7; H, 14,3%). $n_D^{20} = 1{,}4562$; M, 208; Brom. ZahP, 114.

Im Falle $TiCl_3OC_4H_9^{ter}$ sind bestimmt worden: *HCl*; *sec.* C_4H_9Cl Sdp 65–68°; $n_D^{20} = 1{,}3951$. Liter. Sdp 68°; $n_D^{20} = 1{,}3953$; (Ber. für. *sec* C_4H_9Cl: Cl, 38,4; Gef: Cl, 38,6% und *Titanchloroxyd*: Ti, 27–29%; Cl, 42–45% *sec* C_4H_9O, 5–6%). Butylen–Polymer, 11–13%. $n_D^{20} = 1{,}4690$; M, 269; Bromzahl, 196 (Ber. für *n* C_4H_8: C, 85,7; H, 14,30; Gef: C, 85,8; H, 13,73%). Für $TiCl_3OC_6H_{11}$ wurden entsprechend erhalten: HCl, *cyclo*Hexyl–chlorid Spd 140–141°; $n_D^{18} = 1{,}4558$; Lit. Sdp 142°; $n_D^{18} = 1{,}4555$; (Ber. für $C_6H_{11}Cl$: Cl, 29,9; Gef: Cl, 29,5%; und *Titanchloroxyd* Cl 34–37%; Ti 30–32%; *cyclo*Hexen–Verdichtungsprodukt 2–3%. $n_D^{27} = 1{,}4800$; M, 249; Bromzahl, 186, (Ber. für *n* C_6H_{10}: C, 86,80; H, 12,20; Gef. C, 85,54; H, 12,04%). Bei der Synthese $TiCl_3OC_4H_9^{tert}$ als Ergebnis der unverzüglichen Produktzersetzung im Moment seiner Bildung wurde Titanchlorxyd mit folgender Zusammensetzung erhalten: Ti, 25,90; Cl, 47,70%. *iso*Butylen–Polymer 9–10% $n_D^{20} = 1{,}4800$; M, 224; Bromzahl, 260; (Ber. für *n* C_4H_8: C, 85,70; H, 14,30; Gef. C, 84,30; H, 13,10%). Aus der Lösung sind geschieden *tert* C_4H_9Cl Sdp 50–52°, $n_D^{18} = 1{,}3872$; Liter. Sdp 51–52°; $n_D^{15} = 1{,}3869$; (Ber. für *tert*-C_4H_9Cl, Cl, 38,40%; Gef: Cl, 37,80%). und *iso*Butylen–Polymer.

Polymerisation: Polymerisiert wurde in den Ampullen aus Molybdän-Glas, Inhalt ca. 10 cc. Die Beladung mit Katalysator und Monomer erfolgte in der Atmosphäre des gereinigten Stickstoffes, in spezieller Anlage.[5] Zum Polymerisieren wurde die Ampullen in den elektr. Ofen hingelegt, der in einer Schüttelvorrichtung montiert war. Nach der Reaktion wurden die Ampullen geöffnet und das nicht umgesetzte Monomer verdampft. Das gewonnene Polymer wurde vom Katalysator durch Filtriern und Waschen mit destill Wasser getrennt.

Im Falle der Propylen–Polymerisation in Gegenwart von $Al(C_2H_5)_3$ und $TiOCl_2$ wurde das Polymer mit angesäuretem Metylalkohol abgewaschen und in der Luft bei 60° getrocknet. Die Ausbeute des Polymers beträgt 100%.

Hydrochlorieren: Das gemisch von sorgfältig getrockneten Olefinen (Propylen, *iso*Butylen) und HCl wurde durch ein mit Katalysator gefülltes U-Rohr 3–4 Std lang bei der Temperatur 60–65° durchgelassen. Das Erhitzen—im Wasserbad. Die Reaktionsprodukte wurden in den Empfängern kondensiert; die Kühlung für die letzten: Eis und Kohlensaure, gemischt mit Azeton. Das nicht umgesetzte Olefin und HCl wurden aus dem flüssigen Kondensat verdampft der Rest—abdestilliert, die erhaltenen Fraktionen—der Analyse unterworfen.

Das Hydrochlorieren von *cyclo*Hexen erreichte man durch Sättigung der Katalysator-Suspension im Olefin mit Chlorwasserstoff unter ständigem Rühren. Der Lösungsmittel—Überschuss wurde danach abgetrennt, die restliche Flüssigkeit—abdestilliert und analysiert.

[5] G. W. Tkatschenko, P. M. Homikowski und S. S. Medwedew, *J. Physik. Chem. UdSSR* 25, No. 7, 823 (1951).

Tetrahedron, 1959, Vol. 6, pp. 161–165. Pergamon Press Ltd. Printed in Northern Ireland

VOL. 6 1959

At the meeting of the Honorary Editorial Advisory Board in Paris, July 1957, it was decided that the Journal should publish occasionally a résumé of the Life and Work of deceased eminent Organic Chemists.

I. N. NAZAROV 1906–1957

INTRODUCTION*

I. N. NAZAROV was born of peasant stock in the village of Koshelevo in the heart of the country of the middle Volga region. He received his early education at a village school in which he subsequently became a teacher at the age of 17. He was one of the workers and peasants for whom the Soviet government opened the doors of the Universities, and in 1927 he became a student of the Moscow Agricultural Academy named after Timiryazev. This was one of the main seats of chemistry in Russia and associated with the names Kablukov, Pryanishnikov, Williams and Demyanov which inspired young Nazarov.

After graduating from the Academy he decided to devote himself to Organic Chemistry and began his graduate studentship under A. E. Favorsky, at Leningrad University, who suggested to Nazarov that he should study metal ketyls. Favorsky soon recognised the ability of his student. In 1934 the Academy of Sciences was transferred to Moscow, and here Nazarov worked in the newly founded Institute of Organic Chemistry, becoming head of the Vinyl-acetylene Research Laboratory in 1940. In this laboratory—later named the Laboratory of Fine Organic Chemicals—Nazarov worked until the end of his days, and under his leadership gradually developed a team of 60 workers. In 1949 he was elected to the chair of Organic Chemistry of the Moscow Institute of Fine Chemical Technology. Few were better able to set forth material in a systematic and logical fashion and as he himself put it "to make one feel the very nature of matter."

Nazarov received many academic distinctions. In 1940 he was elected corresponding member of the Academy of Sciences of the U.S.S.R. and member of the Academy of Sciences in 1953. He was awarded the Mendeleyev Prize and two Stalin prizes, and was a member of the German Academy of Naturalists (Leopoldina) in Halle, and a corresponding member of the Berlin Academy of Sciences.

He died suddenly on 30th July 1957 in France, after the Sixteenth Congress of Pure and Applied Chemistry in Paris, at which he read four papers. He is survived by his wife and three daughters.

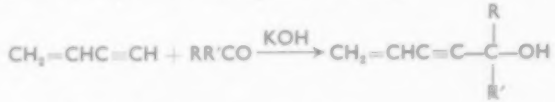
SCIENTIFIC WORK

In his first papers produced in Favorsky's laboratory, Nazarov made a study of the action of sodium on aliphatic and aliphatic-aromatic ketones.

It was established that the stability of metal ketyls of the aliphatic-aromatic series increases with branching of the alkyl substituent in the series $(CH_3, C_2H_5, n\text{-}C_3H_7) < (CH_3)_2CH < (C_2H_5)_2CH$, $(CH_3)_3CH < (C_2H_5)(CH_3)_2C < CH(C_2H_5)_2 < (C_2H_5)_3C$.

Closely related to these studies were the investigations of dissociation and isomerisation of olefines of highly branched structure, published by Nazarov in 1933–1936.

A very important stage in Nazarov's scientific work was connected with the study of the derivatives of vinyl acetylene. The simple method which he devised for the condensation of vinylacetylene with ketones in the presence of potassium hydroxide made accessible various vinylethinylcarbinols, the properties of which were subjected to a comprehensive study.



The principal results of these studies are given in Fig. 1.

* Condensed from the original by L. D. Bergelson.

These investigations, which were stopped by the Second World War when Nazarov and his laboratory were engaged in urgent assignments for the front and the war industry, were resumed with renewed energy after the war.

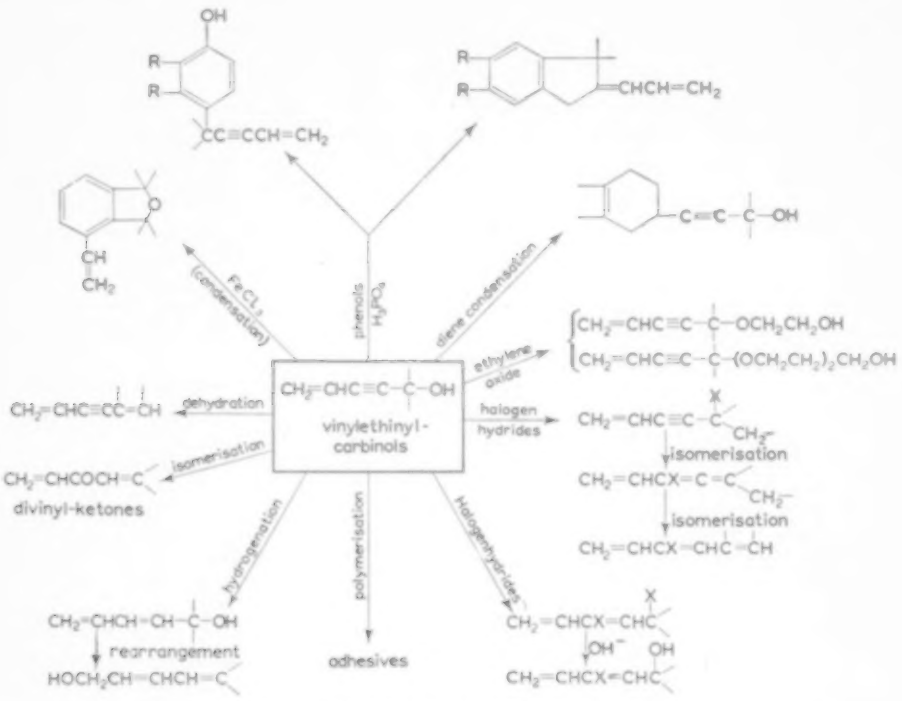
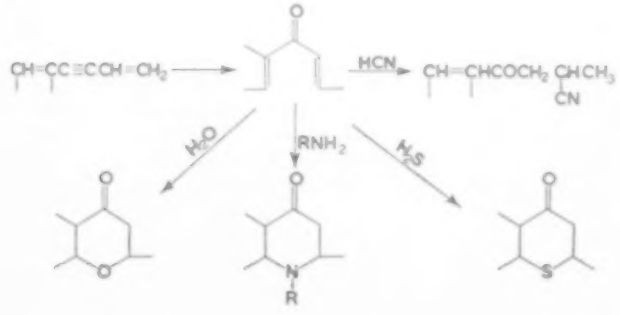


FIG. 1. Reactions of the vinylethinylcarbinols.

Of special interest among the transformations of vinylethinylcarbinols was their isomerisation to reactive divinylketones. A study of the numerous reactions of divinylketones led to a whole range of previously inaccessible compounds (see Fig. 2).

Similar reactions were also carried out with another class of divinylketones synthesised by Nazarov by means of hydration of divinylacetylenes:



Of interest, both theoretically and practically, were the piperidones obtained by reaction of ammonia and amines with divinylketones. The esters of 4-phenyl-piperid-4-ol, synthesised from

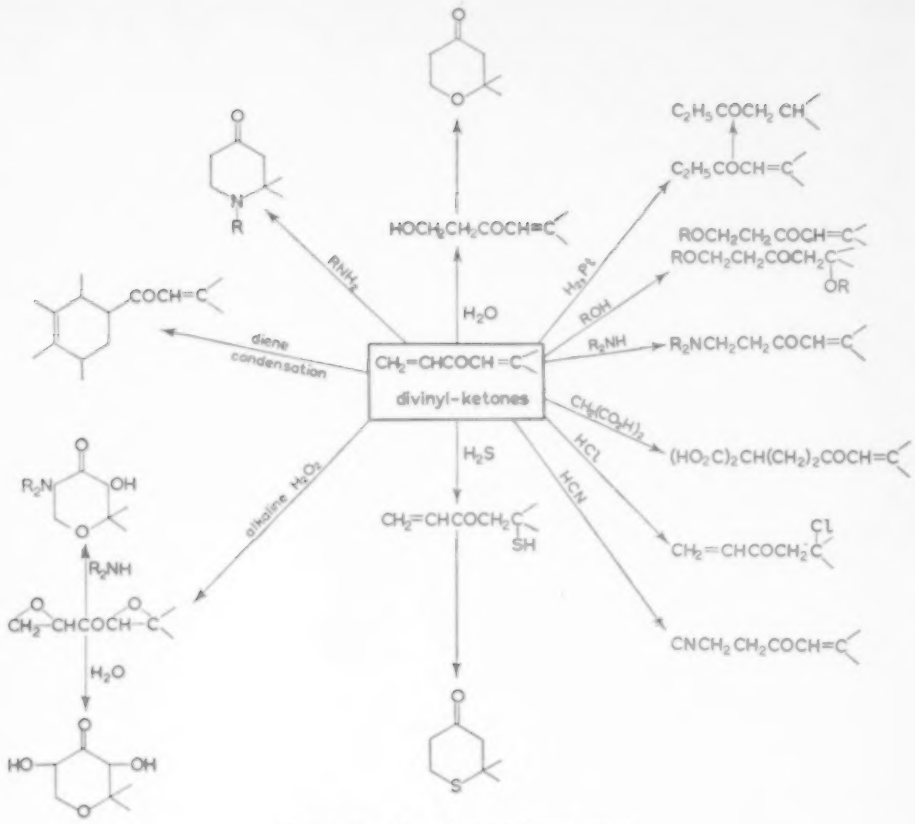
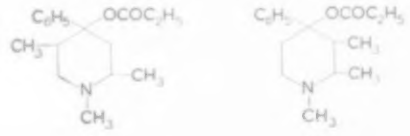


FIG. 2. Transformations of divinylketones.

piperidones, possessed analgesic action. One of them, the hydrochloride of 1:2:5-trimethyl-4-phenyl-piperid-4-ol propionate (I), has a number of advantages over morphine and is widely used in clinics of the Soviet Union under the name of "promedol."



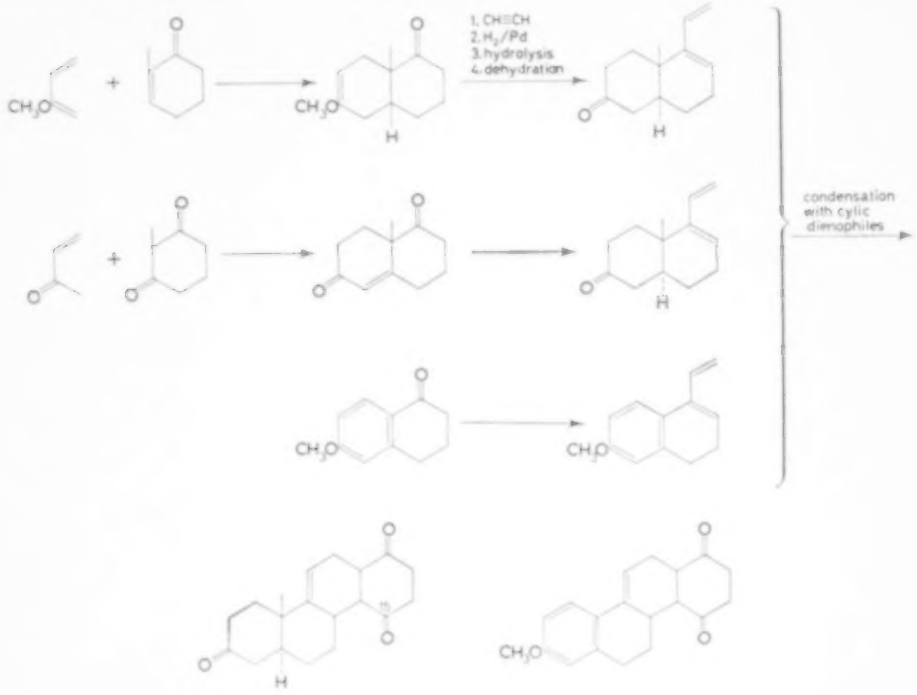
I II

The most active of all presently known analgesics is the hydrochloride of 1:2:3-trimethyl-4-phenyl-piperid-4-ol propionate(II), synthesised by Nazarov. It possesses an activity forty times that of morphine.

Nazarov made a study of the cyclisation of many divinylketones into *cyclo*pentenones and the isomerisation of the latter:

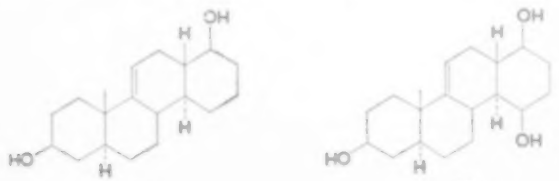
The substituted *cyclo*pentenones entered relatively easily into diene condensation, and this fact served as an impetus to two new independent lines of investigation.

Firstly, certain regularities in diene synthesis and the influence of temperature and other conditions on the reaction, were systematically studied. The quantitative ratio of the isomers formed in a single reaction mixture was shown to be dependent on the structures of the diene and dienophile. Secondly, the polycyclic compounds obtained by means of diene condensation and other reactions were used for the synthesis of substances related to steroids:



III

A detailed study of the condensation of 1-vinyl-Δ^1-octalones and 1-vinyl-6-methoxy-3:4-dihydronaphtalene with unsaturated cyclic ketones showed that the chief products of this reaction were the structural isomers of steroids with "inverted" D rings. For this reason, the condensation of the foregoing dienes with benzo-quinone was used to give tetracyclic compounds related to D-homosteroids.



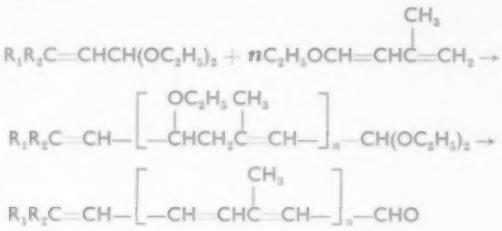
IV V

These tetracyclic ketones were selectively reduced at $C_{(13)}$. In particular, A/B-trans-triketone (III) was converted into the D-homosteroids (IV) and (V), which proved active androgens. In the case of the triol (V), the interesting fact was discovered that the introduction of a hydroxyl group into position 15 increased the androgen activity of the molecule.

New non-steroid estrogens were also obtained, and a study was made of the ways of introducing the dioxyacetone and glycerol side chains of corticosteroids into the polycyclic molecule.

Another part of Nazarov's work was connected with the study of the stereochemistry of certain organic reactions. He investigated the stereochemistry of hydrogenation, oxidation and lactonization of substituted tetrahydrophthalic and octalin-carbonic acids, and the stereochemistry of bromination of acetylenes. A study of the stereochemistry of diene condensations with vinyl*cyclo*hexene and 1(α-acetoxyvinyl)-*cyclo*hexene made possible a stereo-selective synthesis of bicyclic systems.

During the latter years of his life Nazarov was engaged in intensive work on the synthesis of *iso*prenoids. These studies were based on Nazarov's earlier investigations on the anionotropic rearrangement of secondary and tertiary polyene alcohols to primary alcohols, and on the method he discovered of alkali condensation of carbonyl compounds with acetylene under pressure. His work in the field of *iso*prenoids resulted in the synthesis (suitable for industrial production) of the *iso*prenoid alcohols—linalool, geraniol, nerol, nerolidol, farnesol, geranyllinalool, and phytol. A new method was developed of extending the *iso*prenoid chain. It was based on the condensation of acetals with 1-alkoxy*iso*prenes:



Together with his pupils and co-workers Nazarov published over 400 scientific papers. A number of his papers are still unpublished and will appear in the near future. Much of what he had begun was left unfinished and many of his plans were not brought to fruition, for I. N. Nazarov died at the height of his creative work.

L. D. BERGELSON

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BOOK REVIEWS

JEAN MATHIEU and ANDRÉ ALLAIS: **Cahiers de Synthèse Organique. Methodes et Tableaux d'Application.** Vols. 1, 2 & 3, Edited by LÉON VELLUZ. Masson et Cie, Paris, 1957. 232 pp., 322 pp. & 266 pp. respectively.

THESE books are the first of a series of ten to twelve volumes, the object of which is to describe all types of reactions in the field of synthetic organic chemistry. The subject matter is well selected and arranged in a novel and systematic manner. In each volume, each part is preceded by a tabulated synopsis including the code number of the type of reaction involved and the page number, and followed by an elaborate table listing alphabetically numerous examples of each type described. These tables mention the starting materials, the product obtained, the catalyst, yield, reference and code number. Each book also contains an alphabetical index of the chemical functions dealt with. This index is cumulative and includes the material covered in the previous volumes.

At the beginning of each chapter little space only is devoted to the mechanism of the reactions described, but reference is made to a separate volume by the same authors entitled *Principes de synthèse organique* (printed by the same publishers) which deals with the modern theories of organic chemistry. It has thus been possible for the authors to keep the *Cahiers* within reasonable size while at the same time making them easy to consult. The literature coverage is very wide and is complete to 1954–1955.

The title suggests a similarity with *Organic Syntheses*. The object of the work, however, is quite different from that sought by the Editors of *Organic Syntheses*. The *Cahiers* do not describe specific experimental procedures but are more general in nature and classify synthetic organic chemistry according to the reactions involved. They thus possess a pedagogical value to which *Organic Syntheses* cannot pretend, but they cannot quite be considered as a laboratory manual.

In that sense, the title may be slightly misleading. If taken together with the preliminary theoretical volume, the *Cahiers* could be more aptly described as a text of advanced synthetic organic chemistry arranged according to a novel and very rational system.

The volumes are well presented, well printed, easy to read and to consult and should provide a valuable addition to the libraries of all institutions where research in organic chemistry is pursued.

LÉO MARION

Unit Processes in Organic Synthesis (5th Ed.). Editor-in-Chief P. H. GROGGINS. McGraw-Hill, London, New York, 1958. x + 1070 pp. £6. 15s. 6d.

LOOKING it up in GROGGINS has become almost instinctive with students and chemical engineers when faced with a problem in organic synthesis, so the appearance of this new edition is most welcome. The development of the new techniques in this field and the appearance of new organic compounds of industrial importance have both been so rapid in recent years that the book has had to be virtually rewritten and a number of new authors have contributed articles which, taken together, represent a cross-section of present practice in the American organic chemical industry.

Its objective is to provide a wide survey of the various techniques and processes which are available to the chemical engineer in each of the main fields of organic synthesis such as nitration, halogenation, oxidation, hydrogenation, hydrocarbon synthesis, and polymerisation. In each section the methods available are illustrated by a number of examples of the unit processes involved in the production of individual compounds including short descriptions of the plant and the material problems involved in its construction but not attempting to deal with such technical details as heat transfer coefficients or plate efficiencies.

New introductory chapters have been added dealing with the thermodynamics of unit processes and process kinetics and throughout the book much emphasis is rightly placed on the thermodynamics and the kinetics of each process and their influence on the general design of plant, all of which the student will find most valuable.

The chapter devoted to the synthesis of aliphatic hydrocarbons and oxygenated compounds by the Fischer Tropsch and Oxo processes gives in addition to a study of the scientific and economic background of both an up-to-date account of modern developments including a description of the Brownsville and Sasol plants and a survey of the existing Oxo plants in the United States. In view of the rapid progress of polymer science and practice the two chapters dealing with this field of organic synthesis are of special interest and each section has been written by authors directly concerned in this development. The first contains an excellent account of polymer chemistry and of the mechanism and kinetics of the various types of polymerisation. The second deals with a number of the processes in actual operation today for making polymers of different types and with the properties of their products. It thus provides a most useful survey of the polymers that are of industrial importance.

The editor-in-chief has shown his customary skill in the selection of his collaborators and the result is a well-balanced volume covering this wide field in a most illuminating way. It is well documented with references. Its value as a reference book depends to a large extent on the completeness of the index and while in general that seems adequate, there is no reference under acetylene to its production, although this is described on p. 526.

HAROLD HARTLEY

VOL.
6
1959

W. THEILHEIMER: **Synthetic Methods of Organic Chemistry,** Vol. 12. S. Karger, Basel/New York, 1958. XVI + 546 pp., SFr. 92.

THE most depressing aspect of modern science—for those who claim to be scientists—is the speed with which it expands each year. If one considers only a specialised branch of chemistry such as Organic Chemistry, it remains true that there are very few intellects capable of remembering all the pertinent papers published in any one year let alone those which appeared in preceding years. Fortunately only a relatively small proportion of the literature in Organic Chemistry represents really new and significant facts or theories so that if these can be abstracted in some way from the mass of material which, although sound and acceptable on the basis of current publication practice, does not contain any real element of novelty, then one can still hope to keep abreast of the literature. There is, therefore, a real need for review journals and books especially if these are critical in nature.

THEILHEIMER's *Synthetic Methods of Organic Chemistry*, which has now reached the twelfth annual issue, serves a well-known and useful purpose in providing a survey of new methods of real or potential value in synthesis. The volumes also include many examples of known methods applied to new problems. The latter kind of facts are difficult to locate in American Chemical Abstracts and Theilheimer's survey would be justified for this alone. The volume under review, like its predecessors, has a good index and there are many cross-references to earlier volumes in the series. There can be no doubt that the latest volume is a valuable addition to the organic literature.

The most serious criticism that can be made of this book is the question of choice of material and in some cases the uncritical acceptance by the author of interpretations in the literature. Perhaps it would be better if reactions to be included in 'Theilheimer' are submitted by (and to) a panel of experts drawn from the whole of Organic Chemistry. This would help in ensuring that nothing lacking in originality was lost and that the trivial and obvious were more carefully excluded. It would also avoid the occasional repetition of erroneous formulae which are taken from the literature without sufficiently critical appraisal. These remarks are intended to show how 'Theilheimer' could be made even better. The latest volume, like its predecessors, still remains a most useful work of reference.

D. H. R. BARTON

J.-P. MATHIEU and G. OURISSON: **Selected Constants—Optical Rotatory Power. II. Triterpenoids** Pergamon Press, London, 1958. 302 pp., £7.

THIS volume is a companion to that recently published on the rotatory power of steroids, and is an equally valuable compilation. One's confidence in the manner in which this arduous task has been carried out, inspired by the authorship, is not disappointed.

The book begins with an introduction, in English and in French, setting out clearly the way in which the tables are presented and expounding the systems of nomenclature of triterpenes that have been adopted after discussion with other experts. Then follow 160 pages of tables, which list the names of the compounds (arranged according to empirical formulae), melting point, solvent, concentration, temperature, specific rotation for the Na D line, and reference.

The coverage seems to be extraordinarily thorough: no doubt here is the most complete and up to date (end of 1957) bibliography of the literature on triterpenes. The reviewer applied the inevitable test by looking up his own name in the author index to see whether his single publication on triterpenes had been included. Of course it had, but he was surprised to find a second entry against the name, and for a moment was pleased to feel that he had detected the error without which no review is complete. However, examination showed that the entry correctly referred to the optical rotation of a triterpenoid mentioned incidently in a paper on another subject. Thus the tables were turned, and the incident must be recorded as an example of the thoroughness with which the literature has been surveyed.

In the Preface Professor Ruzicka writes that "this book will greatly contribute to promote and to stimulate further work on the triterpenes and I recommend it to all chemists interested in natural products". All readers should echo the words of the father of triterpene chemistry and will urge their librarian to buy a copy, though fewer will wish to pay for one of their own. In spite of the publication being "subsidised by the International Commission of Tables of Constants and by Centre National de la Recherche Scientifique" it costs £7.

The printing, copied by a photographic process from typescript, is sometimes indistinct and tiring to the eye. But these blemishes do not diminish our debt to the compilers of the tables, which will be invaluable to all interested in natural products.

R. C. COOKSON

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RECENT DEVELOPMENTS IN THE CHEMISTRY OF FLAVONOIDS

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Physiological importance

IN recent years, there has been considerable development in the study of vitamin P action and other therapeutic properties of flavonoids.[1,2] Rutin and quercetin have now an established place in therapeutics and are being produced in large quantities. A study of the subject has revealed many possibilities of application. Flavonoids occur in a variety of plants and their extensive use provides opportunity for a new industry based on agriculture.

In food industries such as those of fruit products and beverages, the presence of flavonoids and the various changes they undergo are of importance in regard to taste, flavour, stability and physiological properties. It has been reported by El-Rafey[3] that quercetin enhances the nutritive value of butter.

Flavonoids as antioxidants

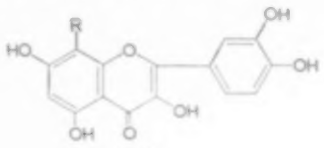
Another direction in which interest has been created is the use of flavonoids as antioxidants. Though reports were made, more than twenty years ago, that quercetin (I) acts an an antioxidant for fats, only recently this subject received attention. Heimann *et al.*[4] suggested that the α:β-unsaturated ketonic structure of the pyrone ring, a free hydroxyl group in the 3-position and free *ortho*-dihydroxy (3′:4′-) grouping in the side phenyl nucleus contribute to the antioxidant activity of quercetin. These structural requirements are similar to those needed for vitamin P properties as recorded earlier.[5]

More recently[6,7] the antioxidant properties of a large number of flavones and flavonols using methyl linoleate have been studied. About the same time a comprehensive study of the antioxidant properties was carried out[8] employing natural fats. There is general agreement between our results and those of other workers.

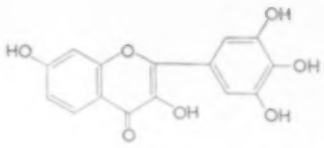
Flavonols are much superior to the other groups of flavonoids and *ortho* and *para* dihydroxy groupings enhance the antioxidant activity; in certain cases the 7:8-dihydroxy system is very favourable. Among the large number of compounds examined, gossypetin (II) and robinetin (III) are compounds of great potency. They are better than quercetin though the latter has the advantage of large availability

[1] J. Q. Griffith, Jr., C. F. Krewson and J. Naghski, *Rutin and related flavonoids'—Chemistry, Pharmacology and Clinical Applications* pp. 1–275. Mack Publishing, Pennsylvania (1955).
[2] G. J. Martin and A. Szent-Györgyi, *Ann. N. Y. Acad. Sci.* **61**, 1–100 (1956).
[3] M. S. El-Rafey, *Wisc. Agri. Exptl. Sta. Bull.* **465**, 33 (1944).
[4] W. Heimann, A. Heimann, M. Gremminger and H. Holland, *Fette u. Seif.* **55**, 394 (1953).
[5] W. G. Clark and T. A. Geissman, *J. Pharm. Exp. Ther.* **95**, 362 (1949).
[6] T. H. Simpson and N. Uri, *Chem. & Ind.* 956 (1956).
[7] C. H. Lea and P. A. T. Swoboda, *Chem. & Ind.* 1426 (1956).
[8] A. C. Mehta and T. R. Seshadri, *J. Sci. Industr. Res. India* In press (1959).

from a number of plant sources. As the result of studies on nuclear oxidation, the conversion of quercetin into gossypetin[9] is easy and good yields are obtained; hence large scale preparation of gossypetin may not offer any difficulty. Robinetin, though not occurring widely in the plant kingdom, can be synthesised by the well known Allan–Robinson condensation. The flavonols should further be considered because of their vitamin P properties.



I, R = H
II, R = OH



III

From the above results relating to antioxidant properties, the occurrence of flavonoids in the heartwoods of plants has considerable significance in connection with their stability to atmospheric oxidation. The toxic properties of these compounds towards fish have already been discussed[10] and they seem to be able to confer resistance to attack by micro-organisms and insects.

It is significant that flavonols are markedly better antioxidants compared with other types. Particular mention may be made that quercetin is much better than taxifolin (dihydroquercetin) though the latter is known to undergo ready oxidation. Based on the free radical theory of autoxidation, the capacity of flavonols (IV) to isomerize into the diketone form (V) seems to provide a possible explanation. The carbon atom in the 2-position will be capable of developing the free electron centre for immobilising free radicals. Catechol and quinol systems in the benzene rings may reinforce the above centre and may also play independent parts as antioxidant groups.

IV V

Biogenesis of flavonoids

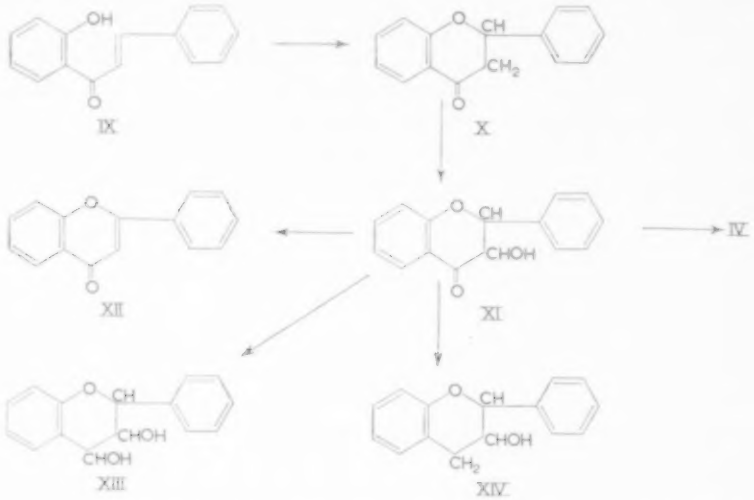
This has been a subject of great interest and the main contributions to our know ledge were made earlier by Robinson[11] who considered the flavonoid (C_{15}) skeleton (VI) to be composed of two parts viz. C_6 and C_9 (VII & VIII).

VII VIII VI

Attempts have recently been made to gain information on the origin of the different parts by employing the tracer technique. The compounds whose syntheses have been

[9] K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 25**, 417 (1947).
[10] T. R. Seshadri, *Ann. Rev. Biochem.* **20**, 490 (1951).
[11] R. Robinson, *Nature, Lond.* **137**, 172 (1936).

studied are quercetin and cyanidin. Underhill *et al.*,[12] followed by others,[13,14] have reported their observations on the biosynthesis of quercetin using buckwheat (*Fagopyrum tataricus*) which produces rutin (quercetin-3-rhamnoglucoside). A number of isotopically labelled (C^{14}) compounds were supplied and the quercetin produced by the plant was decomposed by standard methods. The general indications are that the C_9 and C_6 units have different origins. The latter seem to be produced from acetate units whereas the former seem to arise either from shikimic acid, phenylalanine or cinnamic acid derivatives. The biosynthesis of cyanidin in red cabbage has also been studied[15,16] and the results support the origin of phloroglucinol from acetate units.



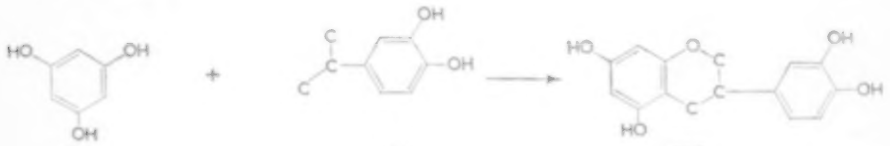
Whatever may be the origin of the C_6 and C_9 units, these seem to be definitely involved in the structure of the flavonoid skeleton.[11] More information has been available in recent years on the inter-relationship between various groups of flavonoids and the possibility of one undergoing change into another. The earliest of the series would appear to be chalkones (IX) and the related flavanones (X). These occur invariably together[17] so long as a phloroglucinol unit with free hydroxyl groups is not present. The flavanone becomes the only stable entity if a 5-hydroxyl group is present in it and this has been attributed to the existence of chelation between this hydroxyl and the neighbouring keto group. A study of the co-occurrence of various groups of flavonoids has revealed important results.[18] The data led to the conclusion that a flavanone (X) can undergo hydroxylation in the 3-position to give rise to a 3-hydroxyflavanone (XI). This reaction has been carried out in a number of ways; the most satisfactory and significant is Fenton's method of oxidation.[19] The hydroxyl

[12] E. W. Underhill, J. E. Watkins and A. C. Neish, *Canad. J. Biochem. Physiol.* **35**, 219, 229 (1957).
[13] T. A. Geissman and T. Swain, *Chem. & Ind.* 984 (1957).
[14] S. Shibata and M. Yamazaki, *Pharm. Bull.* **6**, 42 (1958).
[15] F. Weygand, W. Bruckers, H. Grisebach and E. Schulze, *Z. Naturf.* **B 12**, 222 (1957).
[16] H. Grisebach, *Z. Naturf.* **B 12**, 227 (1957); **B 13**, 335 (1958).
[17] T. R. Seshadri, *Sci. Proc. Roy. Dublin Soc.* **27**, 77 (1956).
[18] T. R. Seshadri, *Les Heterocycles Oxygenes* p. 71. Colloques Internationaux du Centre National la Recherche Scientifique (1955).
[19] V. B. Mahesh and T. R. Seshadri, *J. Chem. Soc.* 2503 (1955).

thus introduced seems to be in the correct conformation for the elimination of water (i.e. *cis* hydrogens) to give a flavone (XII). This conformation is, however, unstable and can undergo change into the more stable *trans*-form which is common in Nature. The stable type undergoes facile dehydrogenation to give rise to flavonols (IV). Thus 3-hydroxyflavanones would appear to hold a key position in the biogenesis of flavonoids. Further, they can be reduced conveniently to yield *leuco*anthocyanidins (XIII),[20,21] which are widely distributed, and also form the catechins (XIV).[22]

3-Phenyl- and 4-phenylchroman derivatives

*iso*Flavones were originally few and considered to be derived from normal flavonoids by a process involving migration of the phenyl group.[23,24] A number of them have later been discovered. Further, we have the same skeleton in pterocarpin and *homo*-pterocarpin[25] and also in angolensin.[26,27] A more recent discovery is that of wedelolactone[28] which is a 3-phenylcoumarin derivative, closely related to the compounds mentioned above. It has, therefore, been suggested[29] that the C_9 forked unit (XV) which is present in all these compounds should be considered as being directly involved in the biogenesis of 3-phenylchroman derivatives (XVI).



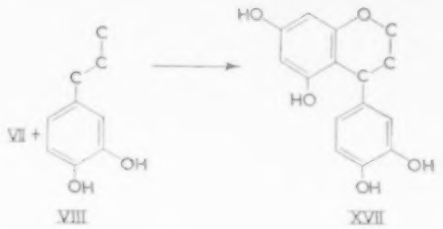
VII XV XVI

Only two compounds were known having a 4-phenylchroman system, namely brazilin and haematoxylin, and Robinson[30,31] originally indicated that they were derived from butein by incorporating a single carbon unit; and the skeleton could be built up on this basis in the laboratory. There has also been the suggestion[32] that their origin involves double migration of phenyl groups starting with the normal 2-phenylchroman structure.

More compounds of this type have recently been found in plants: (i) dalbergin and methyldalbergin in the heartwood of *Dalbergia sissoo*[33] and (ii) calophyllolide in the fruits of *Calophyllum inophyllum*.[34] There seems to be justification for considering that these compounds have an origin independent of the normal flavonoids. Obviously, the linking of C_6 and C_9 (VII & VIII) units can take place in an alternative way to yield 4-phenylchroman derivatives (XVII). The reaction seems to be feasible since,

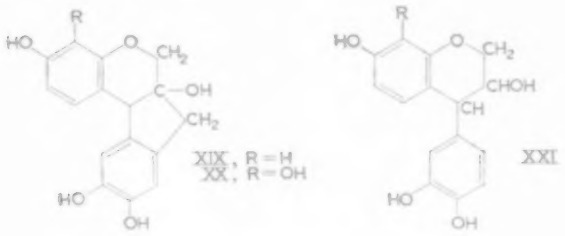
[20] T. Swain, *Chem. & Ind.* 1144 (1954).
[21] A. K. Ganguly and T. R. Seshadri, *Tetrahedron* **6**, 21 (1959).
[22] J. W. Clark-Lewis and W. Korytnyk, *J. Chem. Soc.* 2367 (1958).
[23] T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18**, 165 (1952).
[24] R. Robinson, *The Structural Relations of Natural Products* p. 41. The Clarendon Press, Oxford (1955).
[25] A. McGookin, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 787 (1940).
[26] F. E. King, T. J. King and A. J. Warwick, *J. Chem. Soc.* 1920 (1952).
[27] V. N. Gupta and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 15**, 146 (1956).
[28] T. R. Govindachari, K. Nagarajan and B. R. Pai, *J. Chem. Soc.* 629 (1956).
[29] T. R. Seshadri, *Curr. Sci.* **26**, 239 (1957).
[30] H. G. Crabtree and R. Robinson, *J. Chem. Soc.* **113**, 859 (1918).
[31] R. Robinson, *The Structural Relations of Natural Products* p. 43. The Clarendon Press, Oxford (1955).
[32] W. B. Whalley, *Chem. & Ind.* 1049 (1956).
[33] V. K. Ahluwalia and T. R. Seshadri, *J. Chem. Soc.* 970 (1957).
[34] J. Polonsky, *C. R. Acad. Sci., Paris* **242**, 2961 (1956).

for example, resorcinol reacts with cinnamic acid to yield 7-hydroxy-4-phenyldihydrocoumarin.[35]



VII + VIII → XVII

Since the 4-phenylcoumarins can undergo ready oxidation to benzophenones (XVIII), they are probably intermediates in the formation of the latter. A more satisfactory scheme for the evolution of brazilin (XIX) and haematoxylin (XX) may, therefore, be the incorporation of a single carbon atom into the 4-phenylchroman structure (XXI).[29,32]



XIX; R = H
XX; R = OH

XXI

XVIII XXII XXIII

An interesting and significant property of the 4-phenylcoumarins (XXII) is the colour reaction they give with magnesium and alcoholic hydrochloric acid. Initially an emerald green colour is produced and this changes to a permanent red. The colour seems to be due to the formation of 4-phenylpyrylium salts similar to the flavylium salts. Further, these 4-phenylcoumarins (XXII) exhibit a marked tendency to undergo oxidation with mercuric oxide in alkaline solutions to yield the corresponding coumarilic acids (XXIII).[36]

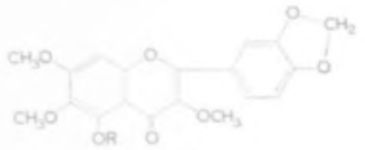
Nuclear oxidation and reduction

Earlier studies of the occurrence of a large number of flavonoids and of their association in plant sources has conclusively established the incidence of nuclear

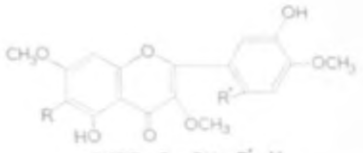
[35] J. D. Simpson and H. Stephen, *J. Chem. Soc.* 1382 (1956).
[36] V. K. Ahluwalia, A. C. Mehta and T. R. Seshadri, *Tetrahedron* **4**, 271 (1958).

oxidation (hydroxylation) in the development of more complex compounds from simpler ones. But no experimental proof was provided about the feasibility of this process and particularly about the reactivity of the molecules in support of this biosynthesis. Many earlier experiments were not successful, but by adopting mild methods and special conditions, Seshadri and co-workers have successfully carried out the nuclear oxidation of a large number of flavonoids. A very important example is the hydroxylation of quercetin to gossypetin[9] on one hand and to myricetin[37] on the other. They have shown that the *para* oxidation is most conveniently effected by alkaline persulphate and the *ortho* oxidation by a two stage process involving aldehyde synthesis and Dakin oxidation. This has led to the convenient preparation, from simpler compounds, of (i) the gossypetin, quercetagetin and calycopterin series of flavonols, (ii) the wogonin, baicalein and nobiletin series of flavones, (iii) chalkones of the pedicin group, (iv) *iso*flavones and (v) anhydro-colour bases like carajurin, and also of many partial methyl ethers occurring in Nature. Reference compounds, needed in the structural studies of naturally occurring anthoxanthin glycosides and partial methyl ethers, can be readily made by the application of these methods. The work has already been reviewed.[38–40]

A more recent extension of this method is the synthesis of the quercetagetin group of flavonols[41] and analogous *iso*flavones.[42] This is particularly useful for the synthesis of certain naturally occurring partial methyl ethers which are difficult to obtain by other methods. Starting from the appropriate 6-hydroxy compounds and introducing a 5-hydroxyl group by the two-stage oxidation, melisimplin (XXIV),[41] melisimplexin (XXV)[41] and oxyayanin-B (XXVI)[43] have been obtained. By applying *para* oxidation in the side phenyl nucleus, oxyayanin-A (XXVII) has been prepared.[44]



XXIV, R = H
XXV, R = CH_3



XXVI, R = OH; R' = H
XXVII, R = H; R' = OH

The possibility of nuclear reduction involving the removal of a phenolic hydroxyl group was also indicated by the survey of anthocyanins and anthoxanthins and the study of their association in Nature. Adequate laboratory analogies, at first sight, seemed to be lacking and hence this process had not been generally recognised as a feasible one. Numerous examples have been recorded in which laboratory reactions involve the loss of a nuclear hydroxyl group.[45]

The following additional cases may be mentioned; boiling hydriodic acid and

[37] K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 28,** 210 (1948).
[38] T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 28,** 1 (1948); **A 30,** 333 (1949).
[39] T. R. Seshadri, *Rev. Pure Appl. Chem. Aust.* **1,** 186 (1951).
[40] T. R. Seshadri, *Experientia Suppl.* II, 258 (1955).
[41] A. C. Jain, T. R. Seshadri and K. R. Sreenivasan, *J. Chem. Soc.* 3908 (1955).
[42] K. Aghoramurthy, T. R. Seshadri and G. B. V. Subramanian, *J. Sci. Industr. Res. India* **B 15,** 11 (1956).
[43] R. N. Goel, A. C. Jain and T. R. Seshadri, *J. Chem. Soc.* 1369 (1956).
[44] N. K. Anand, S. R. Gupta, K. S. Pankajamani and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 15,** 263 (1956).
[45] T. R. Seshadri, *XIV Int. Congress Pure App. Chem. Zurich. Experientia Suppl.* II, 270 (1955).

red phosphorus convert asperthecin[46] into *frangula*-emodin anthranol, and tocopherols[47] lose one nuclear hydroxyl by this treatment. Examples have been recorded among simpler benzene derivatives also. Reduction of 1:2:3:5-tetrahydroxybenzene, its monomethyl ether (iretol) and hexahydroxybenzene with sodium amalgam yields phloroglucinol, and hydroxyquinol gives dihydroresorcinol.[48]

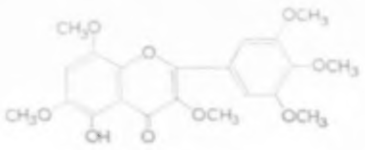
A number of types of compounds have been employed and various reducing agents such as stannous chloride, sodium dithionite, zinc and acetic acid, hydriodic acid and red phosphorus, and sodium amalgam have been used for the direct removal of a hydroxyl group usually from a quinol or a catechol system. A different method, used by Kenner and Murray,[49] involves catalytic reduction (hydrogenolysis) of a tosyl ester using Raney nickel and has been found subsequently to be capable of wide application. Conversion of salicylic acid into benzoic acid,[49] phloroglucinol carboxylic acid into γ-resorcylic acid[50] and orsellinic acid into 6-methylsalicylic acid[51] are typical examples.

The reduction of chrysin to 5-hydroxyflavone and of 3-O-methylgalangin into 5-hydroxy-3-methoxyflavone was carried out almost simultaneously by Ramanathan and Venkataraman;[52] and Jain and Seshadri.[53] This involves the removal of the 7-hydroxyl group. Nuclear reduction in the 5-position giving rise to 7-hydroxy compounds has been reported[54] using as examples, chrysin, apigenin, galangin and quercetin. The hydroxyl groups in the side phenyl nucleus can also be removed[55] i.e. a quercetin derivative is converted into kaempferol and a kaempferol derivative into galangin. Complete removal of hydroxyl groups from the condensed benzene ring as well as the side phenyl nucleus is possible if it is a flavonol derivative, e.g. 3-methoxyflavone can be obtained from 7-hydroxy-3-methoxyflavone; but if there is no substituent in the pyrone ring, further reduction takes place affecting this ring also. 7-Hydroxy- and 5-hydroxy-flavones yield 4-hydroxyflavan.[56,57] Hydroxyxanthones undergo similar nuclear reduction.[58,59] Thus a hydroxyl group in 1- or 3-position can be removed in the case of 1:3-dihydroxyxanthone, yielding 3-hydroxy- and 1-hydroxyxanthone respectively. The successful laboratory preparation of the natural euxanthone (1:7-dihydroxyxanthone) and *allo*euxanthone (3:7-dihydroxyxanthone) from the naturally occurring compound, gentisein (1:3:7-trihydroxyxanthone), further supports the feasibility of nuclear reduction process in Nature. It is also of interest to note that 1-hydroxyxanthone on reduction gives xanthone and not a further reduction product as is obtained in the case of 7- and 5-hydroxyflavones.

The utility of these methods of oxidation and reduction in the synthesis of

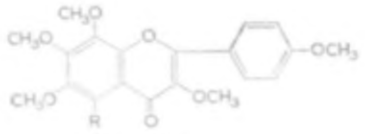
[46] B. H. Howard and H. Raistrick, *Biochem. J.* **59**, 475 (1955).
[47] W. John, E. Dietzel and P. Gunther, *Z. Physiol. Chem.* **252**, 208 (1938).
[48] T. Posternak, *Helv. Chim. Acta* **19**, 1336 (1936).
[49] G. W. Kenner and M. A. Murray, *J. Chem. Soc.* **S**, 178 (1949).
[50] V. Ramanathan and K. Venkataraman, *Curr. Sci.* **21**, 283 (1952).
[51] K. Aghoramurthy, M. K. Ramanathan and T. R. Seshadri, *Chem. & Ind.* 1327 (1954).
[52] V. Ramanathan and K. Venkataraman, *Proc. Indian Acad. Sci.* **A 38**, 40 (1953).
[53] A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 12**, 503 (1953).
[54] A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 38**, 294 (1953).
[55] A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 38**, 467 (1953).
[56] V. N. Gupta, A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 38**, 470 (1953).
[57] J. E. Gowan, S. P. MacGiolla, G. T. MacMohan, S. O'Cleirigh, E. M. Philbin and T. S. Wheeler, *Terathedron* **2**, 120 (1958).
[58] A. C. Jain, O. P. Mittal and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 12**, 647 (1953).
[59] O. P. Mittal and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 14**, 76 (1955).

gardenin (XXVIII), a compound which is otherwise difficult to build up, has already been reviewed.[60]



XXVIII

More recently, a detailed analysis of the peel of a sweet variety of *Citrus aurantium* has revealed the occurrence of auranetin (3:6:7:8:4′-pentamethoxyflavone) (XXIX) and 5-hydroxyauranetin (XXX) together.[61] This may be of significance in biogenesis; the removal of the free hydroxyl of 5-hydroxyauranetin can be smoothly effected by the above method of tosylation and hydrogenation giving rise to auranetin.



XXIX ; R = H
XXX ; R = OH

Nuclear methylation[62]

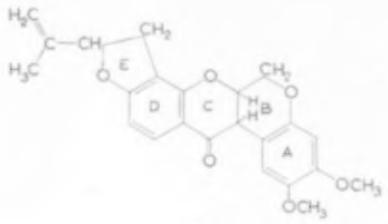
During the ordinary methylation of flavonoids, certain complications arise owing to C-methylation which was noted towards the end of the last century. Based on analogies, the position involved in C-methylation was considered by Baker and Robinson[63] to be 6. The subject has been studied in detail in recent years and the various groups of flavonoids have been examined. It is now established that methylation with methyl iodide and alcoholic potash or better sodium methoxide uniformly gives 6-methyl derivatives. The 8-methyl compounds could be obtained by an alternative method of synthesis using hexamine or similar reagents. The mechanism of these reactions has also been considered; in the first case a β-diketo form of the 5:7-dihydroxyflavonoid seems to be involved and in the second case it is a reaction at an anionoid nuclear position. In Nature one or both of these positions (6 and 8) are found to undergo nuclear methylation and a large number of such compounds have been discovered in recent years. Based on analogy with laboratory experience, it has been suggested that formaldehyde equivalents as well as transmethylating agents can be involved in the process. In the place of methylation, substitution involving dimethylallyl groups is also common and seems to be more facile.

Furan derivatives of flavonoids

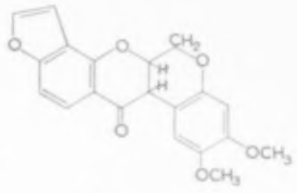
Rotenone and related compounds have been known for a long time. Their valuable selective insecticidal action has made them important. Rotenone (XXXI)

[60] T. R. Seshadri, *Experientia Suppl.* II, 271 (1955).
[61] P. S. Sarin and T. R. Seshadri, *Tetrahedron* To be published.
[62] A. C. Jain and T. R. Seshadri, *Quart. Rev.* **10**, 169 (1956).
[63] W. Baker and R. Robinson, *J. Chem. Soc.* 2713 (1926).

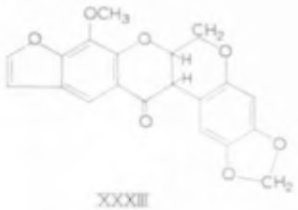
itself has a reduced furan ring with an *iso*propenyl substituent in the α-position. Occurring along with it are other rotenoids which have an unsubstituted furan ring, e.g. elliptone (XXXII)[64] from *Derris elliptica*. In these compounds the fusion of the furan ring to the main skeleton is of the angular type. The alternative fusion of the linear type is also possible as indicated by the isolation of pachyrrhizon[65] (XXXIII) from *Pachyrrhizus erosus*. Harper[66] has recorded that simpler furano-*iso*flavones, in which the oxide ring B was absent, also occurred with rotenoids. Robinson[67] compared rotenone with berberine, brazilin and haematoxylin and made the suggestion that its structure could be derived from the branch chain C_6-C_3-C_6-*iso*flavone skeleton by the addition of one carbon bridge.



XXXI



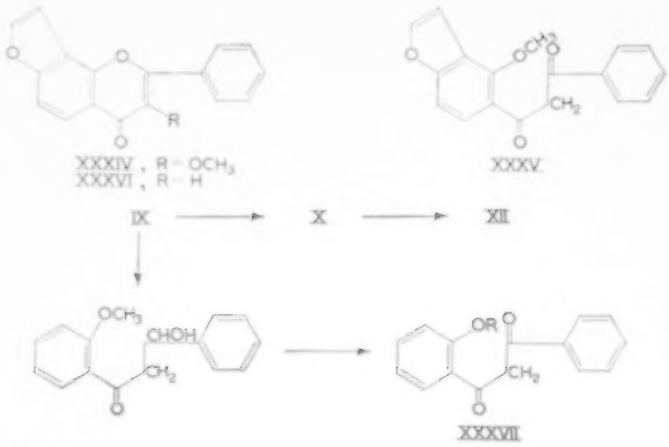
XXXII



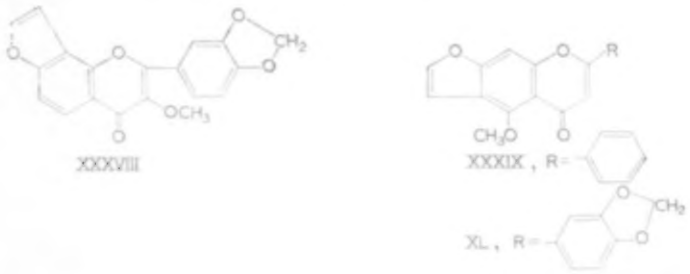
XXXIII

Somewhat later than the rotenoids, flavone derivatives with a fused furan ring were discovered. Karanjin (XXXIV) was the first member to be isolated, studied and synthesised.[68,69] In the seeds of *Pongamia glabra*, pongamol (XXXV) was subsequently found along with karanjin.[70] It is the diketonic analogue[71] of the simplest furanoflavone of the angular type (XXXVI) and its occurrence indicates that the diketone may be a stage in the biosynthesis of flavones. But such combinations are rare and the formation of the diketone seems to be dependent on the *ortho* hydroxyl group being protected by methylation. A more satisfactory explanation of their occurrence would be to consider that both flavones (XII) and diketones (XXXVII) are the result of parallel evolution from chalkones (IX) as shown below.

[64] S. H. Harper, *J. Chem. Soc.* 1099 (1939).
[65] H. Bickel and H. Schmid, *Helv. Chim. Acta* **36**, 664 (1953).
[66] S. H. Harper, *J. Chem. Soc.* 1118 (1940).
[67] R. Robinson, *The molecular architecture of some plant products* p. 11. IX Int. Congress Pure Appl. Chem. Madrid (1934).
[68] D. B. Limaye, *Rasayanam* 1 (1936); 119 (1937).
[69] T. R. Seshadri and V. Venkateswarlu, *Proc. Indian Acad. Sci.* **A 9**, 259 (1939).
[70] S. Rangaswami and T. R. Seshadri, *Curr. Sci.* **9**, 179 (1940).
[71] S. Narayanaswami, S. Rangaswami and T. R. Seshadri, *J. Chem. Soc.* 1871 (1954).



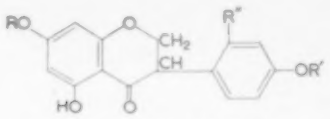
Pongapin (XXXVIII) is another important member of this group and it occurs along with karanjin (XXXIV) in the Australian plant, *Pongamia pinnata*.[72] Present in the same source are gammatin (XXXIX) and pinnatin (XL) which are linear furanoflavones[73] isomeric respectively with karanjin and pongapin.



Pongamol (XXXV) has also been found in the root bark of *Tephrosia lanceolata*[74] (originally called lanceolatin C) along with the simplest furanoflavone (XXXVI) named as lanceolatin B. This discovery is interesting since other *Tephrosia* species are known to contain rotenoids (complex *iso*flavonofuran derivatives). In a related species, *Tephrosia maxima isoflavones* having isoprene units attached have been discovered.[75] These significant observations would suggest that there are common features, particularly as regards the origin of the furan unit.

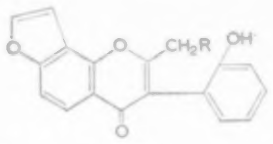
The suggestion[76] seems to be justified that in rotenoids, the *iso*flavone or *iso*flavanone structure constitutes the core of the molecule and the other parts have been built at later stages, and in this connexion may be mentioned the recent isolation of the *iso*flavanones, padmakastein (XLI) (bark of *Prunus puddum*),[77] ferreirin (XLII) and *homo*ferreirin (XLIII) (from the heartwood of *Ferreirea spectabilis*).[78] The oxygen ring in them is of the reduced type, as found in rotenoids (ring C).

[72] L. R. Row, *Aust. J. Sci. Res.* A **5**, 754 (1952).
[73] S. K. Pavanaram and L. R. Row, *Aust. J. Chem.* **9**, 132 (1956).
[74] S. Rangaswami and B. V. R. Sastry, *Curr. Sci.* **24**, 13 (1955).
[75] S. Rangaswami and B. V. R. Sastry, *Curr. Sci.* **23**, 397 (1954); **24**, 337 (1955).
[76] T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.* A **37**, 784 (1953).
[77] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **35**, 202 (1952).
[78] F. E. King, M. F. Grundon and K. G. Neill, *J. Chem. Soc.* 4580 (1952).

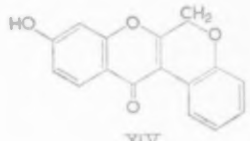


XLI, R = CH_3; R′ = R″ = H
XLII, R = H; R′ = CH_3; R″ = OH
XLIII, R = H; R′ = CH_3; R″ = OCH_3

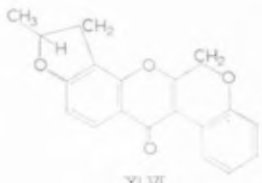
Based on the above-mentioned considerations, simplified methods of synthesis have been developed for building up the 5 ring system of rotenoids. Starting with an *iso*flavone, the intermediate stage would be a 4 ring system, either a furano*iso*-flavone (XLIV)[79] or a chromenochromone (XLV)[76,80] to which the fifth ring could be finally added. A simpler compound having the 5 ring system (XLVI) has been synthesised[81] by the second procedure.



R = OH or halogen XLIV



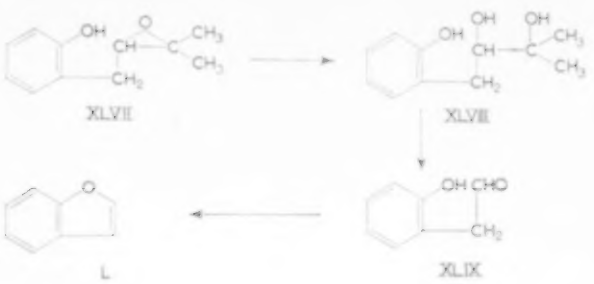
XLV



XLVI

There has been considerable difficulty in the application of the available methods for the construction of a furan ring on to the flavonoid structure. A satisfactory method for this purpose has been recently developed[82] and it is based on considerations of biosynthesis.[83] A careful study of the relationships of furan and other extra skeletal structures present in a variety of naturally occurring substances had led to the conclusion that the C_5 *iso*pentene unit is fundamental and can undergo various modifications. One of these is the capacity to undergo oxidation through the epoxide (XLVII) and glycol (XLVIII) stages, leading to an *o*-hydroxyphenylacetaldehyde system (XLIX); this undergoes ready *cyclo*dehydration to form an unsubstituted furan (L). For laboratory syntheses, such aldehydes are conveniently obtained by ozonolysis or similar treatment of the simpler allyl unit. A study of typical examples (karanjin,[82] pongapin,[82] angelicin,[83] psoralene,[83] visnagin[84] and kellin[85]) has established the full value of this method of approach; good yields of the furano compounds are obtained by the minimum number of steps.

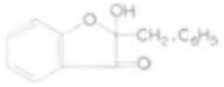
[79] L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 34**, 187 (1951).
[80] A. C. Mehta and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 42**, 192 (1955).
[81] P. S. Sarin, J. M. Sehgal and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 47**, 292 (1958).
[82] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **2**, 203 (1958).
[83] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron*.
[84] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron*.
[85] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 17**, 382 (1958).



XLVII XLVIII L XLIX

3-Hydroxyflavanones

As one of the important lines of recent advances should be mentioned 3-hydroxyflavanones (XI).[86] More than a dozen of these compounds are now known and their constitution established. The main sources are heartwoods and barks of trees. Their isolation and purification are based on their appreciable solubility in water and in ether[87,88] and also on their capacity to form somewhat sparingly soluble salts.[89] They can undergo both dehydration and dehydrogenation giving rise to flavones and flavonols respectively. They are unstable particularly in the presence of alkali and undergo isomeric change into the related 2-hydroxy-2-benzylcoumaran-3-ones (LI).[90] Further change is also possible (involving benzil-benzilic acid change) giving rise to the anhydro-lactones (3-benzalcoumaran-2-ones, LII).[91–93]



LI

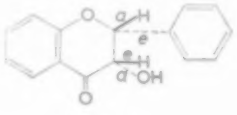
LII LIII

Methylation of 3-hydroxyflavanones has been reported to yield a variety of products.[94,95] Under mild conditions avoiding aqueous medium, it is possible to prepare partial methyl ethers with most or all of the phenolic hydroxyl groups methylated and the alcoholic hydroxyl group free. By prolonged treatment, dehydrogenation and subsequent methylation of the 3-hydroxyl group take place giving rise to the corresponding flavonol methyl ethers. But strong alkaline conditions cause opening of the flavanone ring, leading eventually to the production of methyl ethers of (LI) or (LIII).

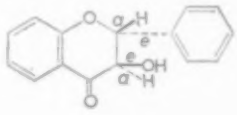
[86] J. E. Gowan, E. M. Philbin and T. S. Wheeler, *The Chemistry of Vegetable Tannins* p. 133. Society of Leather Trades' Chemists, Croydon (1956).
[87] J. C. Pew, *J. Amer. Chem. Soc.* **70**, 3031 (1948).
[88] W. R. Carruthers, R. H. Farmer and R. A. Laidlow, *J. Chem. Soc.* 4440 (1957).
[89] E. F. Kurth, H. L. Hergert and J. D. Ross, *J. Amer. Chem. Soc.* **77**, 1621 (1955).
[90] J. Gripenberg, *Acta Chem. Scand.* **7**, 1323 (1953).
[91] T. Oyemada, *Liebigs Ann.* **538**, 44 (1939).
[92] M. Chadenson, L. Molho-Lacroix, D. Molho and C. Mentzer, *C. R. Acad. Sci., Paris* **249**, 1362 (1955).
[93] J. Gripenberg and B. Jesulius, *Acta Chem. Scand.* **8**, 734 (1954).
[94] W. E. Hillis, *Aust. J. Sci. Res.* **A 5**, 379 (1952).
[95] O. P. Goel, N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 39**, 254 (1954).

The stereochemistry[96] of 3-hydroxyflavanones involves the configuration of the carbon atoms 2 and 3. As a consequence, four optically active and two racemic forms are possible. The natural compounds seem to belong to the *trans* variety and undergo ready dehydrogenation in the presence of alkali or acid and air yielding the corresponding flavonols. This conclusion is supported by the hydrogenation of a (+) taxifolin derivative in the presence of Adams catalyst whereby a (+) catechin derivative is obtained.[22]

A number of methods have been developed for the synthesis of 3-hydroxyflavanones, but the most convenient seems to be the direct hydroxylation of flavanones in the 3-position, either by means of iodine and silver acetate[95,97] or by Fenton's reagent.[19] The synthetic compounds differ markedly from the natural ones in undergoing ready dehydration instead of dehydrogenation. This could be explained as due to the difference in the stereochemistry of the 2- and 3-positions. The synthetic compounds seem to have *cis* hydrogens and the 3-hydroxyl is in the axial conformation (LIV) favourable for the elimination of water. This is also the conformation that could be expected from the substitution reaction employed for the preparation. The *cis*-form is, however, unstable and on treatment with sodium acetate gets converted into the more stable *trans*-form (LV) which is the one occurring in Nature.[96]



LIV



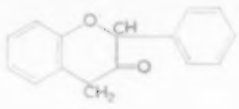
LV

As already mentioned earlier, these compounds are of biogenetic interest since they seem to constitute an essential common step for other groups of flavonoids.

Leuco*anthocyanidins*

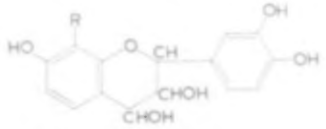
In view of the recent review on this subject,[98] only important points and more recent developments are mentioned here. Rosenheim[99] discovered the existence of *leuco*anthocyanins in the course of his study of the grape vine and the skin of white grapes. He considered them to have the structure of *pseudo*-bases corresponding to the anthocyanins. Robinson[100] made a comprehensive survey of plant materials and found that *leuco*anthocyanidins were widely distributed, either occurring in combination with sugars or free. *Leuco*cyanidins were the most common. He showed that these are not really *pseudo*-bases, and based on their characteristic properties, he suggested that they may have either a flavan-diol (XIII) or the related ketoflavan (LVI) structure. Bate-Smith[101] considered that many plant sources, reported to contain phlobatannins, really contained *leuco*anthocyanidins having probably the flavan-diol structure.

[96] V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **41**, 210 (1955).
[97] R. N. Goel, V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **47**, 184 (1958).
[98] T. Swain and E. C. Bate-Smith, *The Chemistry of Vegetable Tannins* p. 109. Society of Leather Trades' Chemists, Croydon (1956).
[99] O. Rosenheim, *Biochem. J.* **14**, 178 (1920).
[100] G. M. Robinson and R. Robinson, *Biochem. J.* **27**, 206 (1933).
[101] E. C. Bate-Smith, *Biochem. J.* **58**, 122 (1954).



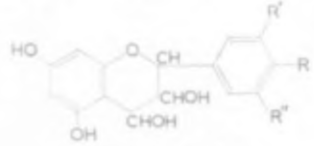
LVI

The first crystalline *leuco*anthocyanidins to be studied were cyanomaclurin and peltogynol, but they had special complexity. King and Bottomley[102] isolated melacacidin from the wood of *Acacia melanoxylon*, prepared a number of derivatives and established its constitution as 7:8:3′:4′-tetrahydroxyflavan-3:4-diol (LVII). This was supported by the synthesis of its tetramethyl ether from 3-hydroxy-7:8:3′:4′-tetramethoxyflavone by hydrogenation using Raney nickel catalyst.[103] Keppler[104] isolated another member of this group, mollisacacidin, from *A. mollissima*. It was shown to have the structure of 7:3′:4′-trihydroxyflavan-3:4-diol (LVIII) and was prepared from fustin by catalytic hydrogenation. But the more widely occurring group of *leuco*anthocyanidins resisted isolation and characterisation. Many of them have now been prepared using certain plant drugs and tanning materials as the most satisfactory sources. The *leuco*anthocyanidins could be obtained in an almost colourless crystalline condition; their partial methyl ethers and acetates are more definitely crystalline and more suitable for physical and chemical studies.



LVII, R = OH LVIII, R = H

(−) *Leuco*pelargonidin (LIX)[105] has now been obtained from *Eucalyptus calophylla* gum (Australian kino). *Butea* gum, another drug, has yielded a (+) *leuco*cyanidin (LX)[21] and tamarind seed testa, a large by-product of industry, another dextrorotatory isomer of the same.[106] Karada bark, a well known tanning material, yields a (−) *leuco*delphinidin (LXI);[107] the gum of *Eucalyptus pilularis* (Nilgiris kino) and the bark of *Phyllanthus emblica* contain a (+) *leuco*delphinidin,[107,108] and a third isomeric (+) *leuco*delphinidin[109] has been obtained from the bark of *Myrica nagi*. All these belong to the flavan-diol type. The results so far obtained show that each *leuco*anthocyanidin can occur in more than one form in Nature.



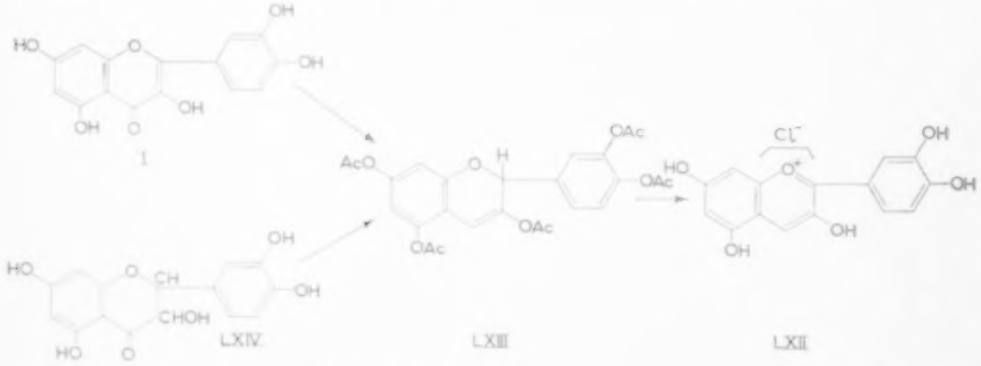
LIX, R = OH; R′ = R″ = H
LX, R = R′ = OH; R″ = H
LXI, R = R′ = R″ = OH

[102] F. E. King and W. Bottomley, *J. Chem. Soc.* 1399 (1954).
[103] F. E. King and J. W. Clark-Lewis, *J. Chem. Soc.* 3384 (1955).
[104] H. H. Keppler, *J. Chem. Soc.* 2721 (1957).
[105] A. K. Ganguly and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 17**, 168 (1958).
[106] K. R. Laumas and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 17**, 44 (1958).
[107] A. K. Ganguly and T. R. Seshadri, *Tetrahedron* **6**, 21 (1959)
[108] K. R. Laumas and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 17**, 167 (1958).
[109] K. R. Laumas and T. R. Seshadri, Unpublished work.

The methods of synthesis of *leuco*anthocyanidins could be considered under two categories: (i) reduction of flavonols and (ii) reduction of dihydroflavonols. The successful synthesis of a *leuco*anthocyanidin by method (i) was made by King and Clark-Lewis[103] who obtained melacacidin tetramethyl ether by the hydrogenation of 3-hydroxy-7:8:3′:4′-tetramethoxyflavone in the presence of Raney nickel. (ii) In the reduction of aromadendrin acetate using lithium aluminium hydride, Bauer, *et al.*[110] isolated a colourless gum which was converted by hot acid in propanol into pelargonidin. Following on this work, Swain[20] reported that the reduction of taxifolin with sodium borohydride gave a non-crystalline *leuco*cyanidin which yielded a hexa-acetate and a tetramethyl ether. The borohydride method has been used as the most convenient, and taxifolin and its methyl ether have been reduced.[21] They yield mixtures of racemates which could be separated by fractional crystallisation. One of these isomers is found to agree with the derivative of the naturally occurring *leuco*cyanidin. Similar reduction of aromadendrin and its methyl ether[111] also gives *leuco*pelargonidin derivatives. Keppler[104] prepared mollisaccacidin by catalytic reduction (Pt catalyst) of the dihydroflavonol, fustin. Freudenberg has used this method for the reduction of a number of dihydroflavonols. An ingenious modification is the use of tetrabenzoyldihydroquercetin to obtain *leuco*cyanidin.[112] In this reaction the benzoyl groups are reduced to benzyl and eventually removed.

In the acetylation of the *leuco*anthocyanidins certain stereoisomers suffered dehydration even in the cold and yielded the corresponding flaven-3-ol acetates.[113] Other stereoisomers did so when the reaction was carried out by heating. These enol acetates have the special characteristic of forming high yields of the corresponding anthocyanidins.

The enol acetate seems to be capable of being formed easily in an unexpected way by the reduction of flavonols. King and White[114] recently carried out the reductive acetylation of flavonols by boiling with zinc dust, acetic anhydride and sodium acetate and thought that the reaction affected only the carbonyl group. From quercetin (I), they obtained an amorphous product to which they gave a constitution which did not agree with the analytical results, but it gave a good yield of cyanidin



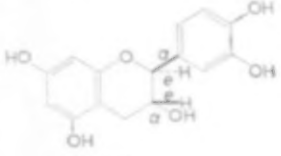
[110] L. Bauer, A. J. Birch and W. E. Hillis, *Chem. & Ind.* 433 (1954).
[111] A. K. Ganguly and T. R. Seshadri, Unpublished work.
[112] K. Freudenberg and K. Weinges, *Angew. Chem.* **70**, 51 (1958).
[113] K. R. Laumas and T. R. Seshadri, *Proc. Indian Acad. Sci.* (1959) under publication.
[114] H. G. C. King and T. White, *J. Chem. Soc.* 3901 (1957).

chloride (LXII) with alcoholic hydrochloric acid. In this respect and in most properties, the reductive acetylation product is found to resemble the flaven-3-ol acetate (LXIII).[113] Obviously the reaction involves reduction of both the ethylene and carbonyl groups followed by the elimination of the elements of water. The same product could be obtained by the reductive acetylation of the dihydroflavonol, taxifolin (LXIV). Quercetin pentamethyl ether also undergoes this reaction. The important point is that these enol derivatives undergo conversion into anthocyanidins in good yields and thus provide better routes for the preparation of anthocyanidins not only from flavonols but also from natural *leuco*anthocyanidins which are known to give very poor yields by direct heating with alcoholic hydrochloric acid.

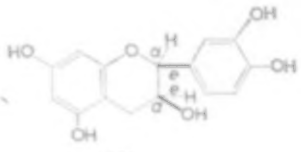
The *leuco*anthocyanidins seem to be capable of ready polymerisation and also of reacting with aldehydic substances to form plastics.[108] In view of their very wide distribution, they could be considered as one of Nature's plastic materials like catechins and lignins. They are definitely capable of combining with proteins.

Catechins

Considerable interest has been shown in the stereochemistry of catechins and the most important of these are (+) catechin (LXV), present in *Gambier catechu*, and (−) *epi*catechin (LXVI) in *Acacia catechu*. Their constitutions are very similar and they have been shown to be stereoisomers of 3:5:7:3′:4′-pentahydroxyflavan. The most significant proofs were provided by the reduction of cyanidin chloride to *epi*catechin (LXVI) and of quercetin pentamethyl ether to *epi*catechin pentamethyl ether and also by the conversion of the catechin into cyanidin chloride (LXII).



LXV



LXVI

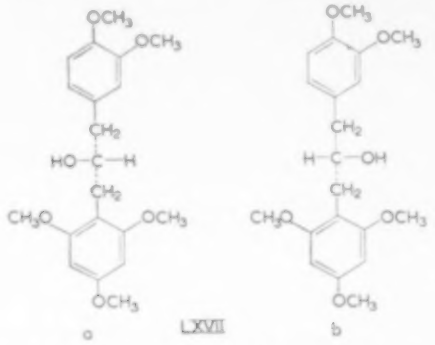
The stereoisomerism involved has been difficult to unravel in all its detail. All the four possible optically active isomers and two racemic compounds are known. The epimerisation from the catechin series to the *epi*catechin series and vice-versa is comparatively easy to carry out. The original suggestion of Freudenberg[115] that this involves change in the 2-position has been unequivocally established.[116] (+) Catechin tetramethyl ether and (−) *epi*catechin tetramethyl ether were subjected to sodium ammonia reduction and by subsequent methylation enantiomorphous pentamethoxy-1:3-diarylpropan-2-ols (LXVIIa & b) were obtained.

This could only be explained if the 3-carbon atoms in (+) catechin tetramethyl ether and (−) *epi*catechin tetramethyl ether have opposite configurations. From this it would follow that (+) catechin and (+) *epi*catechin will have the same configuration at position 3 and the epimerisation takes place by inversion at the 2-position.

The easy formation of a flavene from *epi*catechin was considered to indicate that the hydrogen at C_2 and hydroxyl at C_3 were *trans* to each other favouring smooth

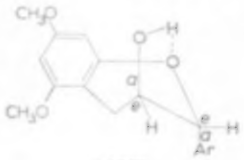
[115] K. Freudenberg, H. Fikentscher and M. Harder, *Liebigs Ann.* **441**, 157 (1925).
[116] A. J. Birch, J. W. Clark-Lewis and A. V. Robertson, *J. Chem. Soc.* 3586 (1957).

elimination of water or in other words the hydrogen atoms in the C_2 and C_3 positions were *cis* to each other (LXVI). Catechin which does not undergo a similar

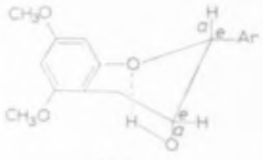


LXVII

change has been assigned the *trans* structure (LXV). In both of them the alcoholic hydroxyl groups are involved in hydrogen bond formation with the ring oxygen and hence are in the axial conformation. The conformation in position 2 then follows as indicated in the formulae (LXVIII and LXIX). It will be noticed that the general expectation that heavier groups would occupy the equatorial positions is not satisfied in these structures. The deviation seems to be due to the hydrogen bond formation leading to the axial disposition of the hydroxyl in the 3-position. Regarding the phenyl group in the 2-position though the two possibilities are found, viz. axial and equatorial, the more widely occurring (−) *epi*catechin has an equatorial phenyl ring. This agrees with the earlier observation that the reduction of cyanidin which has a definitely planar structure gives rise to *epi*catechin.

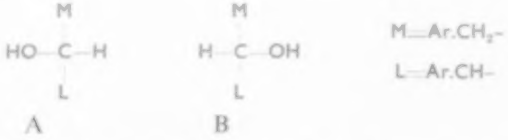


LXVIII



LXIX

The absolute configuration of the alcohols has recently been determined.[116a] In the case of the *cis* compound, (−) epicatechin, the arrangement at the carbon atom 3 was shown to be represented by A and consequently B will represent the arrangement in (+) catechin.

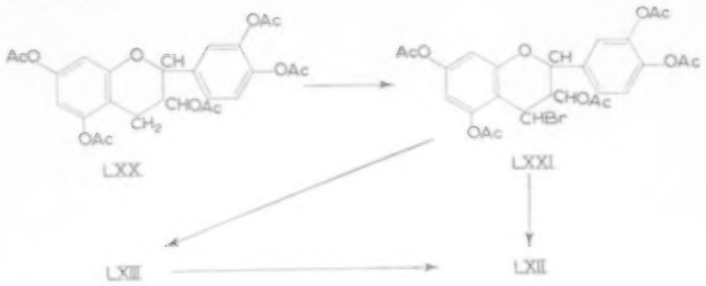


A B

Appel and Robinson[117] effected the conversion of catechin into cyanidin by the action of bromine on the tetramethyl ether in technical dioxan medium. The immediate product was considered to be 8-bromocyanidin bromide tetramethyl ether. A more convenient method of conversion is to brominate the penta-acetates

[116a] E. Hardegger, H. Gempeler and A. Züst, *Helv. Chim. Acta* **40**, 1819 (1957).
[117] H. Appel and R. Robinson, *J. Chem. Soc.* 426 (1935).

(LXX) of (+) catechin and (−) *epi*catechin with NBS; the resulting bromo compound (LXXI) undergoes conversion into cyanidin chloride (LXII) in good yield.[118] With silver acetate, the bromo compound is found to eliminate a molecule of hydrobromic acid and yield *leuco*cyanidin acetate whose analysis and infra-red spectrum suggest a flaven-3-ol formula (LXIII). It gives a good yield of cyanidin chloride (LXII) when boiled with alcoholic hydrochloric acid. Thus the oxidation of catechin has been carried out in stages.



Quinonoid anhydro-bases

Quinonoid anhydro-bases[119] occur widely in the plant kingdom. It was observed by Willstätter and co-workers that anthocyanins change into colour-bases under mild basic conditions (pyridine, aqueous sodium acetate). The colours of these anhydro-bases can vary considerably and depend on the structure of the compounds. The stabler naturally occurring colour-bases are 7-keto derivatives related to flavones and are deep red. The absence of a substituent in the 3-position facilitates the formation of a stable colour-base.

The first known natural compound of this group was carajurin which was isolated by Perkin[120] and which occurs along with another minor component, carajurone, in the rare cosmetic pigment 'Carajura' prepared from the leaves of *Bignonia chica*. The constitution of carajurin ($C_{17}H_{14}O_5$; $2OCH_3$) was established by Chapman, *et al.*[121] Its reactions indicated that it was an anhydro colour-base without a hydroxyl group in the 3-position. Demethylation experiments yielded scutellereinidin chloride (5:6:7:4′-tetrahydroxyflavylium chloride) and boiling with aqueous alkali gave *p*-methoxyacetophenone. These results gave the main skeleton and the position of one of the methoxyl groups. The position of the second methoxyl group was fixed as 5 by eliminating other possibilities and the formula (LXXII) was given to carajurin.

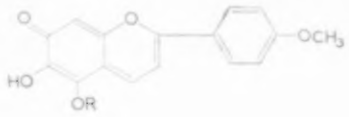
An important point that had not been settled was the possibility of isomeric change during demethylation. It was found[122] that 6:7-dihydroxy-4′-methoxyflavylium chloride was markedly different from 7:8-dihydroxy-4′-methoxyflavylium chloride in the ferric reaction and in the colour and staining capacity of the colour-base. 6:7-Dihydroxy-4′-methoxy-5-methylflavylium chloride resembled the above 6:7-dihydroxy compound as well as carajurin very closely. These results were in agreement

[118] A. K. Ganguly, T. R. Seshadri and P. Subramanian, *Proc. Indian Acad. Sci.* **A 46**, 25 (1957).
[119] T. R. Seshadri, *Naturally Occurring Quinonoid Anhydro-bases*. Festschrift Arthur Stoll. *Experientia* 318 (1956).
[120] A. G. Perkin, *Proc. Chem. Soc.* **30**, 212 (1914).
[121] E. Chapman, A. G. Perkin and R. Robinson, *J. Chem. Soc.* 3015 (1927).
[122] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 37**, 544 (1953).

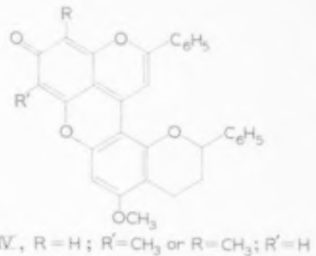
with the constitution of carajurin given above. 7-Hydroxy-5:8:4′-trimethoxyflavylium chloride when subjected to demethylation did not undergo isomeric change under ordinary conditions[123] and the product was different from carajuretin chloride (scutellereinidin chloride).

The synthesis of carajurin has also been achieved[124] by employing an unambiguous series of steps. The important intermediate is 2:4:5-trihydroxy-6-methoxybenzaldehyde which was prepared conveniently by employing the method of nuclear oxidation.

Carajurone, the minor component of Carajura, had one methoxyl group less in its molecule but otherwise resembled carajurin closely. Though no detailed study of the substance could be made, Chapman, *et al.*[121] suggested the possible structure as shown in LXXIII. Its synthesis also offered some difficulty since the isomeric compound with the 5:7:8-arrangement of hydroxyl groups tended to be formed. Finally by employing 2:6-dibenzyloxyquinol and condensing it with anisoylacetaldehyde, carajurone could be synthesised in good yield.[125]



LXXII, R = CH_3
LXXIII, R = H



LXXIV, R = H; R′ = CH_3 or R = CH_3; R′ = H

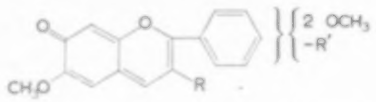
Dragon's blood resin is another source of natural anhydro-bases. This resin is obtained from trees belonging to the genera, *Dracaena* and *Daemonorops* and it contains two substances viz. dracorubin (major component) and dracorhodin (minor component). The latter has a simpler structure; it was shown to be the colour-base of 7-hydroxy-5-methoxy-6-methylflavylium chloride and this constitution was confirmed by synthesis using 2:4-dihydroxy-6-methoxy-5-methylbenzaldehyde and acetophenone.[126,127]

Dracorubin has a more complex structure which has been studied by Brockmann as well as by Robertson *et al.*[128,129] and the latter have given it the formula (LXXIV).

The group of insoluble red woods belonging to the genus *Pterocarpus* provides some of the most valued and durable timbers of the tropical areas. They contain a number of colourless crystalline components belonging to the flavone, *iso*flavone and stilbene groups of compounds. The red colouring matter of these woods has long been an interesting subject of study. Two pigments, santalin (major component) and santarubin (minor component), have been isolated from red woods and tentative structures LXXV and LXXVI respectively for these have been proposed.[130] They

[123] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **38**, 288 (1953).
[124] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **38**, 77 (1953).
[125] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **39**, 45 (1954).
[126] H. Brockmann and H. Junge, *Ber. Dtsch. Chem. Ges.* **76**, 751 (1943).
[127] A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1882 (1950).
[128] H. Brockmann, R. Haase and E. Freienschner, *Ber. Dtsch. Chem. Ges.* **77**, 279 (1944).
[129] A. Robertson, W. B. Whalley and J. Yates, *J. Chem. Soc.* 3117 (1950).
[130] A. Robertson and W. B. Whalley, *J. Chem. Soc.* 2794 (1954).

are also quinonoid anhydro-bases and the flavonoid, *iso*flavonoid and stilbene structures seem to be incorporated in them.

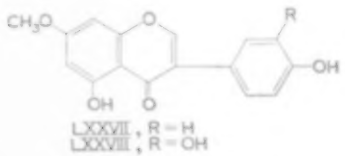


LXXV, R = 3:4-Dimethoxyphenyl; R' = 2:4-dimethoxyphenyl.
LXXVI, R = 2:4-Dimethoxyphenyl; R' = 3:4-dimethoxyphenyl.

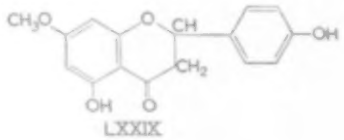
Regarding the relationship between constitution and colour it is significant that the 7-position of the C_{15} unit is involved in the quinonoid structure. This seems to contribute to the stability and the deep red colour of the natural anhydro-bases. Substitution in the 5- and 6-positions with a hydroxyl, methoxyl or methyl group is favourable whereas hydroxy substitution in the 8-position seems to be unfavourable.[131]

Partial methylation and demethylation

In a flavonoid structure, practically all the free positions can contain hydroxyl groups though the 2'- and 6'-positions are rarely occupied in natural compounds. Methylation of these groups seems to be capable of taking place without marked restriction. The more intriguing aspect is the partial methylation of the hydroxyl groups in certain positions leaving the others free. This reaction seems to depend on two important factors: (i) superior reactivity of certain hydroxyl groups and (ii) partial protection of some of them by glycosidation, chelation or complex formation and subsequent methylation. Originally it was considered[132,133] that only in flavanones and *iso*flavones, the hydroxyl group in the 7-position is the most predominantly active and the partial methylation in this position was successfully used for the laboratory synthesis of prunetin (LXXVII),[132] santal (LXXVIII)[134,135] and sakuranetin (LXXIX).[132] This difference seems to exist, though to a lesser extent, in other groups of compounds also. Recently, it has been shown[136] that the partial methylation of the 7-hydroxyl group is possible in certain flavones.



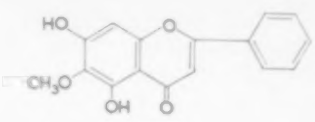
LXXVII, R = H
LXXVIII, R = OH



LXXIX

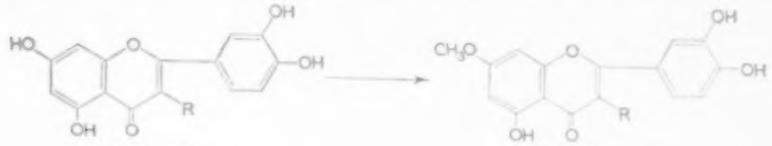
Protection of a reactive hydroxyl by a sugar group, followed by methylation and glycoside hydrolysis was suggested[137] as the possible mechanism for the evolution of oroxylin-A (LXXX) (a 6-methyl ether) and similar compounds in Nature. In these cases, the glycosidic group seems to have been present in the most reactive 7-position.

[131] T. R. Seshadri, *Naturally Occurring Quinonoid Anhydro-bases*. Festschrift Arthur Stoll. *Experientia* 328 (1956).
[132] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 32,** 256 (1950).
[133] T. R. Seshadri, *Ann. Rev. Biochem.* **20,** 507 (1951).
[134] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 32,** 342 (1950).
[135] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 37,** 531 (1953).
[136] T. H. Simpson and J. L. Beton, *J. Chem. Soc.* 4065 (1954).
[137] A. C. Jain, K. S. Pankajamani and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 12,** 127 (1953).



LXXX

The 5-hydroxyl group of most flavonoids is protected by chelation involving the carbonyl group of the pyrone ring. Partial protection of hydroxyl groups in other positions seems to be also possible by complex formation. As an example the borate complexes of hydroxyflavonoids[137,138] may be mentioned. These involve both the chelate structure of the 5-hydroxyl group and the catechol units present in various parts of the molecule. Using this feature, it is possible to prepare partial methyl ethers. Typical examples are rhamnetin[137] (LXXXI) from rutin (LXXXII) or quercetin (I) and 7-O-methylluteolin[139] (LXXXIII) from luteolin (LXXXIV).



I, R = OH
LXXXII, R = O—Rutinosyl
LXXXIV, R = H

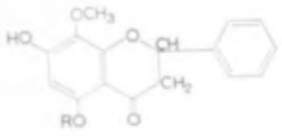
LXXXI, R = OH
LXXXIII, R = H

The naturally occurring partial methyl ethers azaleatin[140] (quercetin-5-methyl ether) and muningin[141] (6:4′-dihydroxy-5:7-dimethoxy*iso*flavone) are extraordinary in that the resistant 5-hydroxyl group is methylated and at the same time more reactive hydroxyl groups are left free. In the flavones, nobiletin and tangeretin, this 5-hydroxyl group is also methylated, but there is otherwise complete methylation. Cases of partial glycosidation of hydroxyl groups in the 5-position are more common (e.g. salipurposide, sakuranin, galuteolin and apigenin-5-glucoside). The explanation offered earlier[142,143] for the evolution of such glycosides is also applicable for the partial methylation as found in azaleatin and muningin. It has been suggested[144] that methylation of the hydroxyl group concerned takes place before pyrone ring closure.

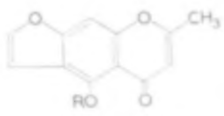
Partial methylation and partial demethylation of flavonoids seem to be related processes and in many cases, the methoxyl groups which arise by methylation of the more acidic hydroxyl groups are those that are less easily demethylated by ordinary methods and vice-versa. A number of reagents have been used by different workers for the partial demethylation of flavonoid methyl ethers. The positions of the methoxyl groups that undergo demethylation depend on the nature of the reagent, the solvent medium and the temperature of the reaction. Methods are available for the selective demethylation of the 5-methoxyl group alone or 3- and 5-methoxyls or 5- and 8-methoxyls or all the methoxyl except that in the 7-position. Typical examples are given below.

[138] M. Shimizu, G. Ohta and T. Yoshikawa, *J. Pharm. Soc. Japan* **71**, 1488 (1951).
[139] K. S. Pankajamani and T. R. Seshadri, *J. Indian Chem. Soc.* **31**, 565 (1954).
[140] E. Wada, *J. Amer. Chem. Soc.* **78**, 4725 (1956).
[141] F. E. King, T. J. King and A. J. Warwick, *J. Chem. Soc.* 96 (1952).
[142] T. R. Seshadri, *Proc. Indian Acad. Sci.* A **32**, 372 (1950).
[143] T. R. Seshadri, *Ann. Rev. Biochem.* **20**, 508 (1951).
[144] M. Krishnamurti and T. R. Seshadri, *J. Sci. Industr. Res. India* B **13**, 474 (1954).

The most convenient reagent which can bring about preferential demethylation of the 5-methoxyl group is anhydrous aluminium chloride in ether solution. This reagent has found wide application in different groups of flavonoids. As an example may be mentioned the recent synthesis of dihydrowogonin (LXXXV)[145] in which 7-hydroxy-5:8-dimethoxy-flavanone (LXXXVI) is subjected to partial demethylation with this reagent in dry ether solution. This provides the most convenient method of synthesis of this naturally occurring flavanone. However, if this reagent is used in nitrobenzene solution, the 3-methoxyl group of flavonols is also demethylated in addition to that in the 5-position.[146] Another demethylating agent of this type is concentrated hydrochloric acid. It has been used in the synthesis of *nor*visnagin (LXXXVII) from visnagin (LXXXVIII)[147] and in the preparation of partial methyl ethers of *iso*flavones.[148] Care has to be taken when hydrobromic acid is used for this selective demethylation because heating at 100° affects the 3-methoxyl group also.[149]

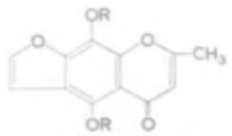


LXXXV, R = H
LXXXVI, R = CH_3



LXXXVII, R = H
LXXXVIII, R = CH_3

In certain cases, where demethylation in both 5- and 8-positions is involved, nitric acid can be used. It forms a 5:8-quinone which can be reduced to the corresponding quinol. The preparation of *nor*kellin (LXXXIX) from kellin (XC)[150] is based on this principle.

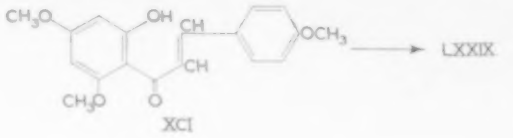


LXXXIX, R = H
XC, R = CH_3

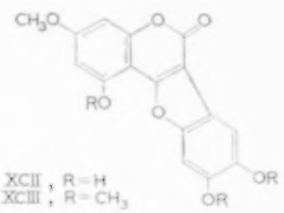
Hydrobromic acid has been found to be a convenient reagent for the demethylation of all the methoxyl groups except the one in the 7-position of flavanones and *iso*flavones. For example, sakuranetin (LXXIX) can be prepared from 2-hydroxy-4:6:4′-trimethoxychalkone (XCI).[151] A more satisfactory reagent for the *iso*flavones is hydriodic acid which is employed under controlled conditions. By this means, the naturally occurring *iso*flavones, prunetin (LXXVII)[152] and santal (LXXVIII),[134,135] have been synthesised. A recent example of the utilisation of this method of partial demethylation is the preparation of wedelolactone (XCII) from its full methyl ether

[145] S. N. Aiyar, I. Dass and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **46**, 238 (1954).
[146] K. V. Rao and T. R. Seshadri, *J. Chem. Soc.* 771 (1946); 122 (1947).
[147] A. Schönberg and N. Badran, *J. Amer. Chem. Soc.* **73**, 2960 (1951).
[148] M. L. Dhar, N. Narasimhachari and T. R. Seshadri, *J. Sci. Industr. Res. India* B **14**, 73 (1955).
[149] R. C. Shah, V. V. Virkar and K. Venkataraman, *J. Indian Chem. Soc.* **19**, 135 (1942).
[150] V. V. S. Murty and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **30**, 107 (1949).
[151] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **29**, 265 (1949).
[152] N. Narasimhachari, T. R. Seshadri and S. Sethuraman, *Proc. Indian Acad. Sci.* A **36**, 194 (1952).

(XCIII).[153] Other methods of synthesis involving protection of hydroxyl groups by other means are far more difficult.



XCI



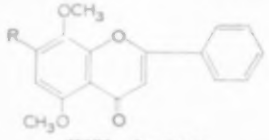
XCII, R = H
XCIII, R = CH_3

Ring isomeric change in flavonoids

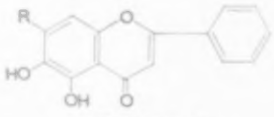
In a number of cases of flavonoids, two isomers can arise as the result of the pyrone ring closing in two different ways. Both isomers occur in a few natural sources, but this is not general. The question then arises as to whether both are produced from a common precursor by ring closure in two ways or a factor of special stability plays a part favouring one structure. The alternative would be the process of direct substitution of a precursor in two different ways. Hence the study of isomeric change under laboratory conditions may be of value.

Mukerjee and Seshadri[154] reviewed this subject in detail. It was emphasised that the pyrone ring can open even in hot acid solutions and can thus provide conditions suitable for isomeric change. The earlier work of Wessely and Moser[155] and many others[156–158] related to the conversion of 5:7:8-methoxyflavones (XCIV) into the 5:6:7-hydroxy compounds (XCV) during demethylation with hydriodic acid. This was of importance from the point of view of the determination of structure. Rao, *et al.*[159] utilised this reaction for synthetic purposes. A similar position existed also with 5:8-dimethoxy compounds (XCVI) undergoing change into the 5:6-dihydroxy compounds (XCVII).[160,161]

In chromones and flavones the above isomeric change took place with considerable



XCIV, R = OCH_3
XCVI, R = H



XCV, R = OH
XCVII, R = H

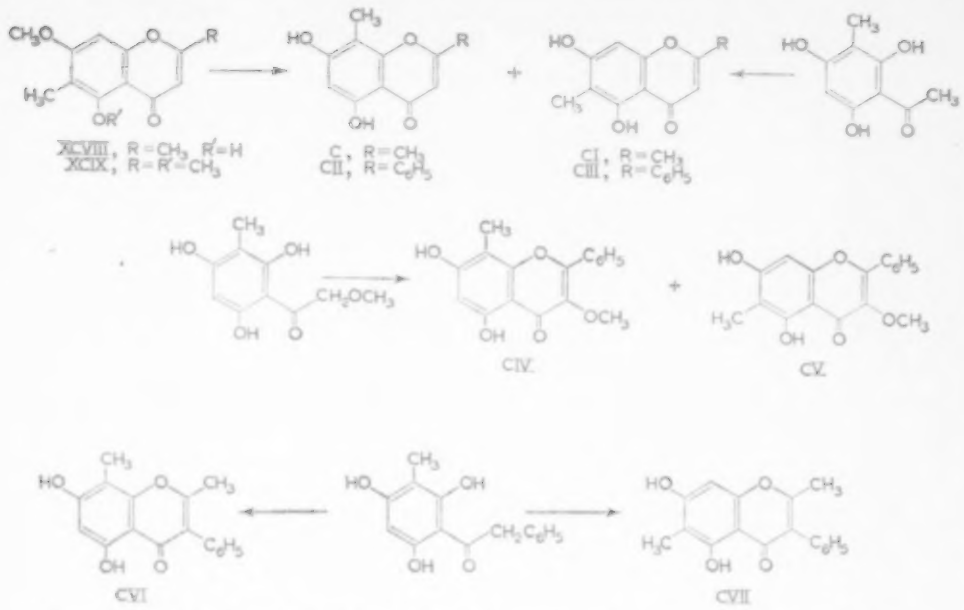
[153] N. R. Krishnaswamy and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 16**, 268 (1957).
[154] S. K. Mukerjee and T. R. Seshadri, *Chem. & Ind.* 271 (1955).
[155] F. Wessely and G. H. Moser, *Monatsh.* **56**, 97 (1930).
[156] F. Wessely and F. Kallab, *Monatsh.* **60**, 26 (1932).
[157] R. C. Shah, C. R. Mehta and T. S. Wheeler, *J. Chem. Soc.* 1555 (1938).
[158] V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 24**, 245 (1946).
[159] K. V. Rao, T. R. Seshadri and N. Viswanadham, *Proc. Indian Acad. Sci.* **A 29**, 72 (1949).
[160] W. Baker, N. C. Brown and J. A. Scott, *J. Chem. Soc.* 1922 (1939).
[161] A. Ballio and F. Pocchiari, *Ric. Sci.* **20**, 1301 (1950).

facility. The reverse change was not found to happen. Using select examples, Seshadri and co-workers[162–164] showed further that substitution in the 3-position is of importance, a methoxy, hydroxy or phenyl substituent prevents this isomeric change under ordinary conditions of demethylation while a methyl group does not. This was explained as due to their influence on the reactivity of the 2-position. The work of Wheeler and co-workers[165] and of Baker *et al.*[166] showed that even this effect can be overcome by employing drastic conditions, i.e. high temperature in a sealed tube. The preferential formation of the 5:6:7-arrangement of hydroxyl groups during demethylation was attributed to the greater stability of this arrangement[167] and this was also supported by similar preferential formation of flavones and flavonols of this type when the method of synthesis (e.g. Allan–Robinson method) can lead to the production of both isomers.

The position is rather more complex when C-methylchromone and flavone derivatives are employed. Schmid[168] first noticed that the 6-methylchromone derivatives, eugenitin (XCVIII) and its methyl ether (XCIX) underwent isomeric change into the 8-methyl derivative (C) by demethylation with hydriodic acid. But in the Kostanecki–Robinson condensation, the 6-methyl compound (CI) was reported to be obtained exclusively.[167,168] Later work by Mukerjee and Seshadri[169] showed that mixtures were obtained in both reactions, but in the former, the 8-methyl compound (C) was the most predominant and in the latter, the 6-methyl compound (CI). In the case of the corresponding flavones, both demethylation and Allan–Robinson condensation led to almost equal quantities of the mixture (CII & CIII).[170,171] On the other hand with C-methylflavonols, though the synthesis gives mixtures containing almost equal amounts of the isomers (CIV & CV), demethylation with hydriodic acid under ordinary conditions brings about no isomeric change[172] owing to the stabilising effect of the 3-hydroxyl group. In the synthesis of *iso*flavones, the 8-methyl compounds (CVI) are generally formed if the temperature of the reaction is high[173] (boiling acetic anhydride) whereas if the reaction is conducted at 0°, the 6-methyl compounds (CVII) result.[174] The position is slightly different in the case of 6- or 8-methoxy*iso*flavones. Ordinary methods seem to favour the formation of the 8-methoxy compounds[166] whereas under special conditions the 6-methoxy isomers are obtained.[175]

Recently, experiments have been conducted in order to follow up the isomeric change when all the four positions of the condensed benzene ring are substituted and there is one methyl or hydroxyl group in the 6- and 8-positions.[176,177] It was

[162] T. R. Seshadri, S. Varadarajan and V. Venkateswarlu, *Proc. Indian Acad. Sci.* A **32**, 250 (1950).
[163] N. Narasimhachari, L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **35**, 46 (1952).
[164] S. K. Mukerjee, T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.* A **35**, 82 (1952).
[165] D. M. X. Donnelly, E. M. Philbin and T. S. Wheeler, *Chem. & Ind.* 163 (1954).
[166] W. Baker, I. Dunstan, J. B. Harborne, W. D. Ollis and R. Winter, *Chem. & Ind.* 277 (1953).
[167] S. K. Mukerjee, T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.* A **37**, 127 (1953).
[168] H. Schmid, *Helv. Chim. Acta* **32**, 813 (1949).
[169] S. K. Mukerjee and T. R. Seshadri, *Chem. & Ind.* 1009 (1955).
[170] S. K. Mukerjee and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **38**, 207 (1953).
[171] N. R. Bannerjee and T. R. Seshadri, *J. Sci. Industr. Res. India* B **13**, 598 (1954).
[172] A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res. India* B **12**, 564 (1953).
[173] R. Iengar, A. C. Mehta, T. R. Seshadri and S. Varadarajan, *J. Sci. Industr. Res. India* B **13**, 166 (1954).
[174] A. C. Mehta and T. R. Seshadri, *J. Chem. Soc.* 3823 (1954).
[175] S. A. Kagal, S. S. Karmarkar and K. Venkataraman, *Proc. Indian Acad. Sci.* A **44**, 36 (1956).
[176] S. K. Mukerjee, T. R. Rajagopalan and T. R. Seshadri, *J. Sci. Industr. Res. India* B **16**, 58 (1957).
[177] V. V. S. Murty, T. R. Seshadri, V. Sundaresan and B. Venkataramani, *Proc. Indian Acad. Sci.* A **46**, 265 (1957).



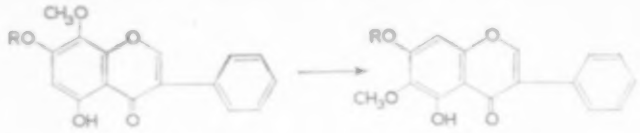
observed that the 5:6:7-trihydroxy-8-methyl compound (CVIII) was the stable form and the 6-methyl compound (CIX) underwent isomeric change on treatment with hot hydriodic acid. A hydroxyl in the 6- and a methyl group in the 8-position seem to provide the more stable structure.

Flavylium salts have not been fully investigated but the results obtained so far suggest that contrary to expectation, based on the analogy of the flavones, the 5:7:8-arrangement of hydroxyl groups is more favoured during the synthesis, and subsequent demethylation does not bring about any change under ordinary conditions.[123] Recently Wheeler *et al.*[178] have reported the isomeric change of 5:7:8-substituted flavylium salts into 5:6:7-substituted ones under drastic conditions.

In the case of chromones and flavones, the isomeric change was studied only in boiling acid solutions since under mild alkaline treatment they do not undergo change and on boiling in alkaline solutions they undergo fission. With *iso*flavones, the position is different. Under mild alkaline conditions, the *iso*flavone system undergoes isomeric change. The first example to be studied was the conversion of 5-hydroxy-7:8-dimethoxy*iso*flavone (CX).[179] Subsequently, modifications[180,181] have been

[178] D. M. X. Donnelly, P. B. Green, E. M. Philbin, F. T. B. Smyth and T. S. Wheeler, *Chem. & Ind.* 892 (1958).
[179] V. B. Mahesh, N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **39**, 165 (1954).
[180] M. L. Dhar and T. R. Seshadri, *J. Sci. Industr. Res. India* B **14**, 422 (1955).
[181] V. B. Mahesh and T. R. Seshadri, *J. Sci. Industr. Res. India* B **14**, 671 (1955).

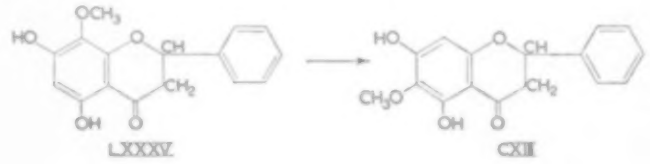
employed and it has been found possible to isomerise satisfactorily 5:7-dihydroxy-8-methoxy*iso*flavone (CXI) into the more difficultly available 6-methoxy compound (CXII).[182] This method is capable of useful application.



CX, R = CH_3
CXI, R = H

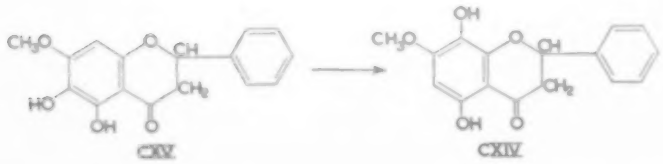
CXII, R = H

The flavanone ring structure is susceptible to opening in mild acid as well as alkaline conditions and hence isomeric change takes place readily. The earliest example was the conversion of carthamidin into *iso*carthamidin when heated with water.[183] With flavanones having fewer number of hydroxyl groups, mild alkali in the cold can be used. This treatment was employed by Narasimhachari and Seshadri[184] to test the stability of the 5-hydroxyflavanone derivatives. More recently, Chopin *el al.*[185] have used it for converting 5:7:8-substituted flavanones into 5:6:7-substituted flavanones. For example, dihydrowogonin (LXXXV) was changed into dihydro-oroxylin (CXIII) when dissolved in alkali and subsequently acidified. But a new observation was made by them that in the case of 5:8-dihydroxy-7-methoxy-flavanone (CXIV) there is no isomeric change in acid or alkaline medium; in fact, the isomeric 5:6-dihydroxy-7-methoxyflavanone (CXV) is more unstable and undergoes change into the 5:8-dihydroxy isomer (CXIV). This was attributed to chelation between the 8-hydroxyl and the pyrone oxygen stabilising this isomeric form. The 7-methoxyl group is considered to be essential for this stability of the quinol as otherwise the 7-hydroxy compound behaves in the normal way and undergoes isomeric change.



LXXXV

CXII



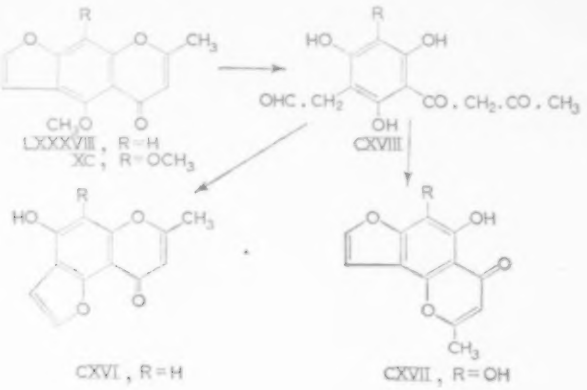
CXV

CXIV

The unexpected difference in the behaviour of the closely related furanopyrones, visnagin (LXXXVIII) and kellin (XC), when subjected to demethylation, has already been mentioned.[154] It is now definite that the formation of *noriso*visnagin (CXVI)[186]

[182] M. L. Dhar and T. R. Seshadri, Unpublished work.
[183] C. Kuroda, *J. Chem. Soc.* 752 (1930).
[184] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **28**, 223 (1948).
[185] J. Chopin, D. Molho, H. Pachéco and C. Mentzer, *C. R. Acad. Sci., Paris* **243**, 712 (1956).
[186] J. R. Clarke, G. Glaser and A. Robertson, *J, Chem. Soc.* 2260 (1948).

involves the rearrangement of the furan ring whereas the formation of *norisokellin* (CXVII)[187] involves the rearrangement of the pyrone ring. More recent studies[84] on the synthesis of furanopyrones lead to the conclusion that both the rings open in acid medium (CXVIII) and rearrangement takes place involving one or the other ring depending on structural factors.



It should be emphasised that the methods of demethylation and methylation can influence structure. As indicated above, demethylation with hydriodic acid can bring about isomeric change in a large number of cases; to avoid this, anhydrous aluminium chloride is the reagent of choice. It seems to be clear that in the more stable structures (flavones, chromones and *iso*flavones) methylation does not produce any isomeric change but with flavanones, the position is different. Aqueous alkali and dimethyl sulphate are unsuitable because of ring opening. There are indications that even methylation with dimethyl sulphate, acetone and potassium carbonate can produce isomeric change.[188]

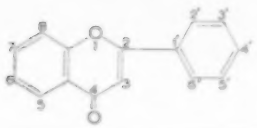
Though in general we could anticipate the manner in which isomeric change would take place in the many systems investigated, the position is not definite and predictable. Hence, adequate caution has to be exercised in drawing conclusions based on the experimental results.

New discoveries

In an earlier review,[189] a list of naturally occurring flavonoids was presented and they were arranged according to the well known groups. During the intervening period, there has been a large number of new discoveries and a few cases of correction of the old constitutions. Hence, the additional matter in this regard is provided in the following tables with the recent references from which the earlier references could be traced.

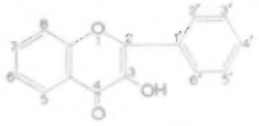
[187] S. K. Mukerjee and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 13,** 400 (1954).
[188] H. G. Krishnamurti and T. R. Seshadri, Unpublished work.
[189] T. R. Seshadri, *Ann. Rev. Biochem.* **20,** 491 (1951).

FLAVONES



Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(1) Tectochrysin[190]	5	7	*Pinus and Populus* species
(2) 5:6-Dimethoxyflavone[191]	–	5,6	*Casimiroa edulis*
(3) Tangeretin[192] (Ponkanetin[193,194])	–	5,6,7,8,4′	*Citrus poonensis*
(4) 5-O-Desmethylnobiletin[61]	5	6,7,8,3′,4′	*Citrus aurantium*
(5) Strobochrysin[170]	5,7	(6-methyl)	*Pinus strobus*

FLAVONOLS

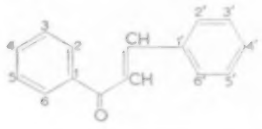


(1) Rhamnocitrin[146]	3,5,4′	7	*Rhamnus catharticus*
(2) Tamarixetin[195]	3,5,7,3′	4′	*Tamarix troupii*
(3) Azaleatin[140]	3,7,3′,4′	5	*Rhododendron mucronatum*
(4) Ombuin[44]	3,5,3′	7,4′	*Phytolacca dioica*
(5) Ayanin[196]	5,3′	3,7,4′	*Distemonanthus benthamianus.*
(6) Flindulatin[197]	5	3,7,8,4′	*Flindersia maculosa.*
(7) Penduletin[198]	5,4′	3,6,7,	*Brickelia pendula.*
(8) Limocitrin[199]	3,5,7,4′	8,3′	*Citrus limon.*
(9) Ternatin[200]	5,4′	3,7,8,3′	*Melicope ternata.*
(10) Oxyayanin-B[45]	5,6,3′	3,7,4′	*Distemonanthus benthamianus.*
(11) Chrysosplenetin[201]	3,5,4′	6,7,3′	*Chrysosplenium japonicum.*
(12) Polycladin[202]	5,4′	3,6,7,3′	*Policlados abietinus.*
(13) Artemisetin[203]	5	3,6,7,3′,4′	*Artemisia* species.
(14) Oxyayanin-A[44]	5,2′,5′	3,7,4′	*Distemonanthus benthamianus.*
(15) 5-Hydroxyauranetin[61]	5	3,6,7,8,4′	*Citrus aurantium.*

[190] V. B. Mahesh and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 13,** 835 (1954).
[191] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4170 (1956).
[192] L. J. Goldsworthy and R. Robinson, *Chem. & Ind.* 47 (1957).
[193] J. M. Sehgal, T. R. Seshadri and K. L. Vadhera, *Proc. Indian Acad. Sci.* **A 42,** 252 (1955).
[194] S. Matsuura, *J. Pharm. Soc. Japan* **77,** 328 (1957).
[195] R. N. Goel and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 47,** 191 (1958).
[196] F. E. King, T. J. King and K. Sellars, *J. Chem. Soc.* 92 (1952).
[197] R. F. C. Brown, P. T. Gilham, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7,** 181 (1954).
[198] S. E. Flores and J. Herran, *Tetrahedron* **2,** 308 (1958).
[199] R. M. Horowitz, *J. Amer. Chem. Soc.* **79,** 6561 (1957).
[200] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 864 (1950).
[201] T. Nakaoki and N. Morita, *J. Pharm. Soc. Japan* **76,** 320 (1956).
[202] G. B. Marini-Bettolo and St. Chiavarelli, Abstracts of papers presented at the XVI Int. Congress Pure Appl. Chem. Paris, p. 212 (1957).
[203] L. Y. Mazur and A. Meisels, *Bull. Res. Council Israel* **A 5,** 67 (1955).

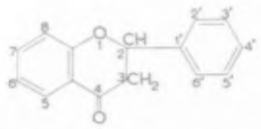
Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(16) Desmethoxykanugin[204]	–	3,7(3′:4′-methylene-dioxy)	*Pongamia glabra.*
(17) Melisimplin[41]	5	3,6,7(3′:4′-methyl-enedioxy)	*Melicope simplex.*
(18) Melisimplexin[41]	–	3,5,6,7(3′:4′-methyl-enedioxy)	*Melicope simplex.*
(19) Meliternatin[205]	–	3,5(6:7:3′:4′-bis-methylenedioxy)	*Melicope ternata.*
(20) Pinoquercetin[206]	3,5,7,3′,4′	(6-methyl)	*Ponderosa* pine bark.
(21) Pinomyricetin[206]	3,5,7,3′,4′,5′	(6-methyl)	*Ponderosa* pine bark.
(22) Persicarin[207]	5,7,3′,4′	(3-potassium sulphate)	*Polygonum hydropiper.*
(23) Persicarin-7-methyl ether[208]	5,3′,4′	7(3-potassium sulphate)	*Eonanthe stolonifera.*
(24) Distemonanthin[209]	5,7,4′	6(6′-3-lactone)	*Distemonanthus benthamianus.*

CHALKONES

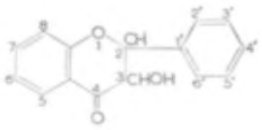
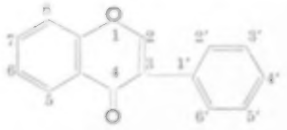


(1) *iso*Liquiritigenin[17]	2,4,4′	–	Liquorice roots, *Dahlia* spp.
(2) *iso*Liquiritigenin-4-methyl ether[210]	2,4′	4	*Xanthorrhoea* resins.
(3) Excelsin[190]	2	4,6	*Pinus excelsa.*
(4) Stillopsidin[211] (*neo*plathymenin)	2,4,5,3′,4′	–	*Plathymenia reticulata, Coreopsis stillmanii.*
(5) Okanin (*trans*) & *iso*-okanin[212] (*cis*)	2,3,4,3′,4′	–	*Cyclicodiscus gabrinensis.*
(6) Lanceoletin[213]	2,4,3′,4′	3	*Coreopsis* species.

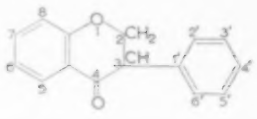
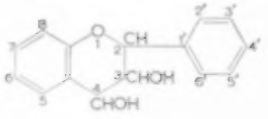
FLAVANONES



[204] O. P. Mittal and T. R. Seshadri, *J. Chem. Soc.* 2176 (1956).
[205] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 3131 (1951).
[206] R. Mani, V. Ramanathan and K. Venkataraman, *J. Sci. Industr. Res. India* B **15**, 490 (1956).
[207] H. Tatsuta and Y. Cochii, *J. Chem. Soc. Japan* **75**, 941 (1954).
[208] H. Tatsuta, *J. Chem. Soc. Japan* **75**, 939 (1954).
[209] F. E. King, T. J. King and P. J. Stokes, *J. Chem. Soc.* 4594 (1954).
[210] H. Duewell, *J. Chem. Soc.* 2562 (1954).
[211] K. R. Laumas, S. Neelakantan and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **46**, 343 (1957).
[212] F. E. King and T. J. King, *J. Chem. Soc.* 569 (1951).
[213] M. Shimokoriyama and S. Hattori, *J. Amer. Chem. Soc.* **75**, 1900 (1953).

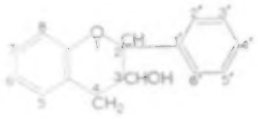
Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(1) Pinocembrin[190]	5,7	–	*Pinus* species.
(2) Alpinetin[214]	7	5	*Alpinia chinensis.*
(3) Pinostrobin[190]	5	7	*Pinus* strobus.
(4) 5:4′-Dihydroxy-7:3′-dimethoxy flavanone[213]	5,4′	7,3′	*Melicope sarcococca.*
(5) 5-Hydroxy-7:3′-dimethoxy-4′-prenyloxyflavanone[213]	5	7,3′(4′-prenyloxy)	*Melicope sarcococca.*
(6) Dihydrowogonin[215]	5,7	8	*Prunus avium.*
(7) Plathymenin[216]	6,7,3′,4′	–	*Plathymenia reticulata.*
(8) 8-Methoxybutin[213]	7,3′,4′	8	*Coreopsis grandiflora.*
(9) Strobopinin[217]	5,7	(6-methyl)	*Pinus strobus.*
(10) Cryptostrobin[217]	5,7	(8-methyl)	*Pinus strobus.*
(11) Ferrerol[218]	5,7,4′	(6,8-dimethyl)	*Rhododendron farrerae.*
(12) Cyrtominetin[219]	5,7,3′,4′	(6,8-dimethyl)	*Cyrtomium* species.
3-HYDROXYFLAVANONES			
(1) Pinobanksin[190]	3,5,7	–	*Pinus strobus.*
(2) Pinobanksin-7-methyl ether[185] (alpinone)	3,5	7	*Pinus excelsa, Alpinia japonica.*
(3) Aromadendrin 7-methyl ether[220]	3,5,4′	7	*Eucalyptus maculata* kino.
(4) Dihydrorobinetin[96]	3,7,3′,4′,5′	–	*Robinia pseudacacia.*
(5) Dihydrorhamnetin[221]	3,5,3′,4′	7	*Prunus puddum.*
(6) Dihydroquercetin-3′-methyl ether[96]	3,5,7,4′	3′	*Abies concolor.*
(7) Dihydromorin[88]	3,5,7,2′,4′	–	*Morus lactea.*
(8) Dihydroherbacetin-8:4′-dimethyl ether[222]	3,5,7	8,4′	*Prunus mume.*
(9) Strobobanksin[96]	3,5	7(6-methyl)	*Pinus strobus.*
*iso*FLAVONES			

[215] V. B. Mahesh, S. Neelakantan and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 15**, 287 (1956).
[216] T. A. Geissman, *Aust. J. Chem.* **11**, 376 (1958).
[216] F. E. King, T. J. King and K. G. Neill, *J. Chem. Soc.* 1055 (1953).
[217] R. N. Goel and T. R. Seshadri, Unpublished work.
[218] R. H. Arthur, *J. Chem. Soc.* 3909 (1955).
[219] Y. Kishimoto, *Pharm. Bull.* **4**, 24 (1956).
[220] R. J. Gell, J. T. Pinley and E. Ritchie, *Aust. J. Chem.* **11**, 372 (1958).
[221] R. N. Goel and T. R. Seshadri, *Tetrahedron* In press.
[222] M. Hasegawa, Private communication.

Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(1) Muningin[223]	6,4′	5,7	*Pterocarpus angolensis.*
DIHYDRO*iso*FLAVONES			
(1) Padmakastein[224]	5,4′	7	*Prunus puddum.*
(2) Ferreirin[78]	5,7,2′	4′	*Ferreirea spectabilis.*
(3) *Homo*ferreirin[78]	5,7	2′,4′	*Ferreirea spectabilis.*
AURONES			
(1) Palasetin[17]	6,3′,4′	–	*Butea frondosa, Cosmos sulphureus. Dahlia variabilis.*
(2) Leptosidin[225]	6,3′,4′	7	*Coreopsis* species.
(3) Aureusidin[226]	4,6,3′,4′	–	*Oxalis cernua, Antirrhenium majus.*
*leuco*ANTHOCYANIDINS (flavan diols)			
(1) Mollisacacidin[104] (Gleditsin[227])	7,3′,4′	–	*Acacia mollisima. Gleditsia japonica.*
(2) Melacacidin[102]	7,8,3′,4′	–	*Acacia melanoxylon.*
(3) *leuco*Pelargonidin[105]	5,7,4′	–	*Eucalyptus calophylla* gum.
(4) *leuco*Cyanidin[21]	5,7,3′,4′	–	*Butea* gum, Tamarind seed testa.

[223] M. L. Dhar and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **43,** 79 (1956).
[224] S. Ramanujam and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **47,** 175 (1958).
[225] T. A. Geissman and W. Moje, *J. Amer. Chem. Soc.* **73,** 5765 (1951).
[226] T. A. Geissman and J. B. Harborne, *J. Amer. Chem. Soc.* **77,** 4622 (1955).
[227] J. W. Clark-Lewis and M. Mitsuno, *J. Chem. Soc.* 1724 (1958).

VOL. 6 1959

Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(5) *leuco*Delphinibin[195]	5,7,3′,4′,5′	–	Karada bark, *Eucalyptus pilularis* gum.
CATECHINS			
(1) (—) *epi*Afzelechin[225]	5,7,4′	–	*Afzelia* species.

[225] F. E. King, J. W. Clark-Lewis and W. F. Forbes, *J. Chem. Soc.* 2948 (1955).

Tetrahedron, 1959, Vol. 6, pp. 201 to 216. Pergamon Press Ltd. Printed in Northern Ireland

α-HYDROXYALKYLIDEN-LACTON-UMLAGERUNG—IX*

SYNTHESE DES D,L-IRIDOMYRMECINS UND VERWANDTER BICYCLISCHER LACTONE

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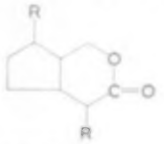
Chemisches Institut der Universität Bonn

(*Received* 23 *October* 1958)

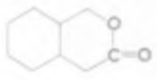
Zusammenfassung—Es wird über allgemein anwendbare Synthesen berichtet, die zum D, L-Iridomyrmecin und ihm verwandter bicyclischer γ- und δ-Lactone führen.

Abstract—Generally applicable synthesises which lead to D, L-iridomyrmecin and related bicyclic γ and δ-lactones are reported.

UM die von Korte *et al.*[1] aufgefundene α-Acyl-Lactonumlagerung auch bei bicyclischen Lactonen durchführen zu können, ergab sich die Notwendigkeit der Darstellung von Lactonen des Typus I, II, III, IV.

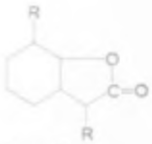


I, R=H
Ia, R=CH_3



II

III



IV, R=H
IVa, R=CH_3

Die Synthese dieser Lactone gewann noch an Interesse durch die Auffindung des Ameisenkampfstoffes Iridomyrmecin (Ia) durch Pavan,[2] dessen Struktur von Fusco *et al.*[3] aufgeklärt wurde. Neben seiner insektiziden Wirksamkeit zeigt dieser Stoff antibiotische Eigenschaften gegenüber Typhus-, Paratyphus-, Cholera- und Tuberkelerregern. Ferner isolierten Cavill *et al.*[4] ein Isomeres des Iridomyrmecins aus einer verwandten australischen Ameisenart und zeigten, dass sich Iridomyrmecin in dieses *iso*Iridomyrmecin umlagern lässt. Für die Synthese dieser bicyclischen Lactone erwiesen sich vier Verfahren als geeignet, die im folgenden beschrieben werden.

* VIII Mitteilung: F. Korte and K. H. Löhmer, *Chem. Ber.* **91**, 1397 (1958).

[1] F. Korte, H. Machleidt und K. H. Büchel, *Chem. Ber.* **90**, 2137, 2150, 2280 (1957); F. Korte und H. Machleidt, *Ibid.* **88**, 1676 (1955).

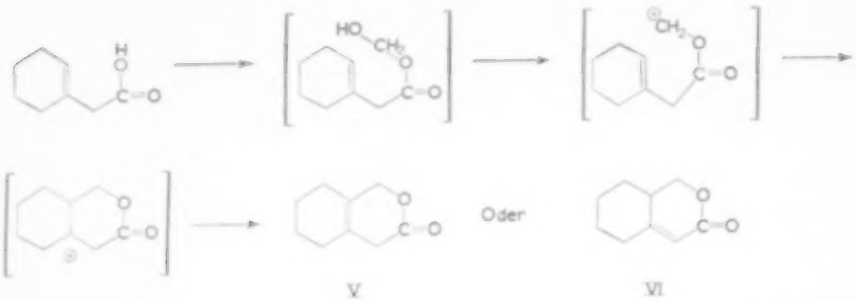
[2] M. Pavan, *Ric. Sci.* **19**, 1011 (1949); **20**, 1853 (1950); *Chim. e Industr.* **37**, 625 und 714 (1955).

[3] R. Fusco, R. Trave und A. Vercellone, *Chim. e Industr.* **37**, 251 und 958 (1955).

[4] G. W. K. Cavill, D. L. Ford und H. D. Locksley, *Aust. J. Chem.* **9**, 288 (1956); **10**, 352 (1957).

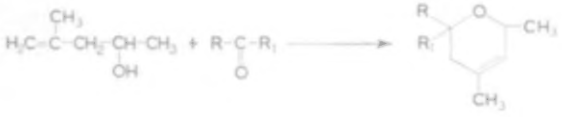
1. *Darstellung mit Hilfe der Prins-Reaktion*

Im Rahmen von Arbeiten über Erythrina-Alkaloide beschrieb Belleau[5] erstmalig die Anwendung der Prins-Reaktion[6] zur Synthese bicyclischer Lactone. Er ging dabei von *cyclo*Hexenessigsäure aus und erhielt nach Umsatz mit Paraformaldehyd in Abhängigkeit vom Lösungsmittel die Lactone V oder VI. Einen entsprechenden



V VI

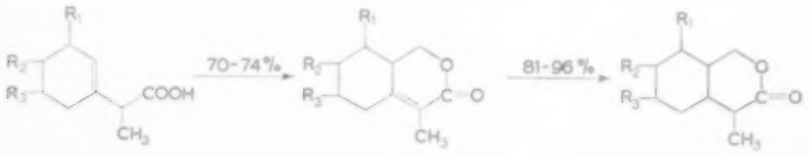
Reaktionsmechanismus formulieren Williams *et al.*[7] bei der Darstellung substituierter Dihydropyrane aus ungesättigten Alkoholen und Carbonylkomponenten mit Hilfe der Prins-Reaktion:



Die Prins-Reaktion erschien uns zur Darstellung bicyclischer δ-Lactone allgemein geeignet. Durch katalytische Hydrierung erhielten wir aus VI das gewünschte gesättigte bicyclische Lacton II.

Auf Grund unserer Erfahrung an monocyclischen ungesättigten Lactonen benutzten wir als Katalysator Raney-Nickel in Aethanol, da mit Edelmetallkatalysatoren der Lactonring leicht Hydrogenolyse erleidet.[1]

Wir stellten so in der *cyclo*Hexanreihe, ausgehend von den Verbindungen VII *a*, *b*, *c* und *d*, die bicyclischen Lactone IX *a*, *b* und das Gemisch aus IX *c* und *d* dar. Sowohl die Prins-Reaktion in Eisessig/Schwefelsäure als auch die Hydrierung gelingen in guten Ausbeuten. In Abwesenheit von Paraformaldehyd tritt mit Eisessig Schwefelsäure eine Isomerisierung von VII zu den Lactonen vom Typ IV ein.



VII VIII IX

[5] B. Belleau, *Canad. J. Chem.* **35**, 673–676 (1957).
[6] H. J. Prins, *Chem. Weekblad* **14**, 932 (1917); **16**, 1072, 1510 (1919); *Proc. Acad. Sci. Amster.* **22**, 51 (1919); J. W. Baker, *J. Chem. Soc.* 296 (1944), 89 (1948); W. Barendrecht, *Chem. Weekblad* 54, 404, 414 (1958).
[7] P. H. Williams, G. C. Ecke und S. A. Ballard, *J. Amer. Chem. Soc.* **72**, 5738 (1950).

VII. VIII. IX *a*: $R_1, R_2, R_3 = H$

b: $R_1, R_3 = H, R_2 = CH_3$

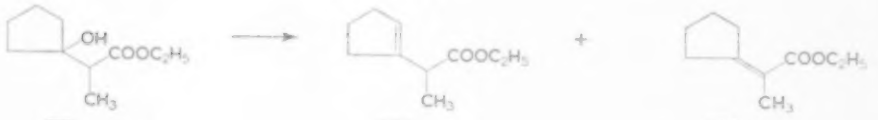
c: $R_1 = CH_3, R_2, R_3 = H$

d: $R_1, R_2 = H, R_3 = CH_3$

Bei Uebertragung der Reaktion auf *cyclo*Pentenderivate sollte Iridomyrmecin zugänglich sein. Wir erwarteten eine Ausbeuteverminderung, da nach den Ergebnissen von Brown[8] bei 5-gliedrigen Ringen die exocyclische Doppelbindung (XIV) leichter ausgebildet wird als bei 6-gliedrigen Ringen, wo die endocyclische Doppelbindung (XI) den Vorrang hat. Es stand also zu befürchten, dass unter unseren Reaktionbedingungen bevorzugt der α-β-ungesättigte Ester (XXI) statt des β-γ-ungesättigten Esters (XIX) entsteht. Mit Substanzen vom Typ XXIV gelingt die Prins-Reaktion jedoch nicht mehr, wie unsere Versuche zeigten.

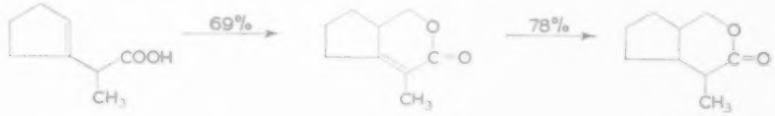
In Uebereinstimmung mit den Ergebnissen von Brown[8] führt die Wasserabspaltung bei dem Hydroxyester X vollständig zum β-γ-ungesättigten Ester XI,[9] während bei der Wasserabspaltung aus XII neben dem für die Prins-Reaktion benötigten β-γ-ungesättigten Produkt XIII auch der α-β-ungesättigte Ester XIV entsteht.[10]

X XI



XII XIII XIV

Das Estergemisch wird verseift und die α-β-ungesättigte Säure durch Destillation abgetrennt. XV lässt sich mit Hilfe der Prins-Reaktion glatt zu XVI umsetzen.



XV XVI XVII

Zur Synthese des Iridomyrmecins gingen wir von 3-Methyl-*cyclo*-pentanon aus, das nach Reformatzky mit α-Brompropionsäureäthylester zu dem Hydroxyester XVIII umgesetzt wurde. Die Wasserabspaltung lieferte daraus ein Gemisch der ungesättigten Ester XIX, XX, XXI. Nach der alkalischen Verseifung lässt sich die Säure XXIV durch Destillation abtrennen. XXII, XXIII wurden mit Paraformaldehyd in Eisessig/Schwefelsäure zu den ungesättigten Lactonen XXV, XXVI umgesetzt, die

[8] H. C. Brown, *J. Amer. Chem. Soc.* **76,** 467 (1954); *J. Org. Chem.* **22,** 439 (1957).
[9] O. Wallach und E. Evans, *Liebigs Ann.* **360,** 44 (1908).
[10] O. Wallach und K. V. Martius, *Liebigs Ann.* **365,** 272 (1909).

katalytisch zu einem Gemisch aus I *a* und XXVII hydriert wurden. Ein aufgenommenes Gaschromatogramm bestätigt das Vorhandensein von mindestens zwei Substanzen. (Beckman GC-2,200 Milliampere, H_2-Druck 1 atü, Temp 160°, Empfindlichkeit 10, Einsatz ca. 70–80 mg, Kolonne Nr. 70008).

VOL.
6
1959

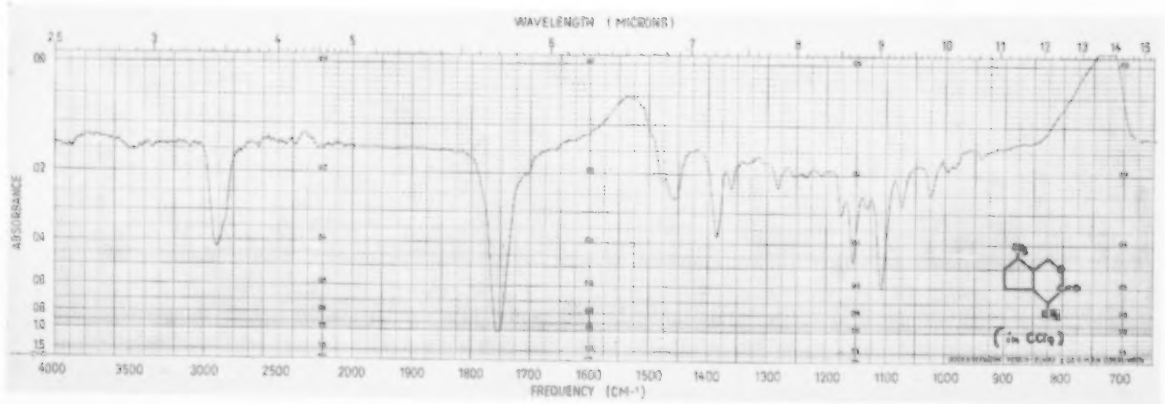


Abb. 1.—IR-Spektrum des synthetischen D, L-Iridomyrmecins.

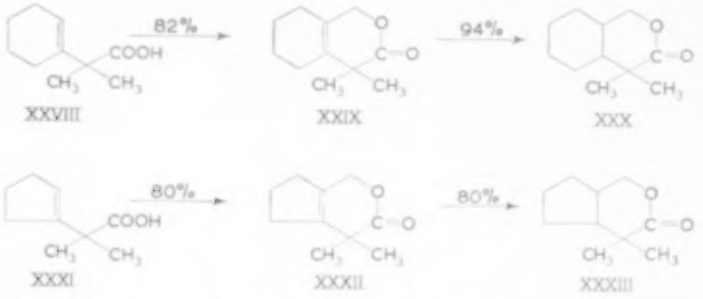
Aus diesem Gemisch konnte das D, L-Iridomyrmecin durch Zugabe eines Impfkristalles* auskristallisiert werden, während die restliche Substanz als Oel zurückblieb.

Das synthetisierte kristalline D,L-Iridomyrmecin ist in seinen chemischen, physikalischen und biologischen Eigenschaften sowie dem IR-Spektrum mit dem von Pavan isolierten Produkt identisch. Es liegt als Racemat vor.

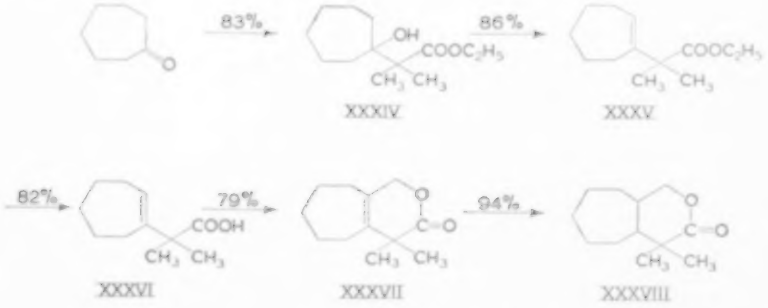
Mit dieser Synthese ist die Struktur des Iridomyrmecins endgültig gesichert (Abb. 1).

Während Belleau bei der Prins-Reaktion in Abhängigkeit vom Lösungsmittel neben VI auch V erhielt, fanden wir bei allen Versuchen unabhängig vom Lösungsmittel nur das Auftreten von α-β-ungesättigten Lactonen sowohl in der 5- als auch in der 6-Ringreihe. Das geht besonders aus der Betrachtung der UV-Absorption hervor, die bei allen Produkten ein λ_{max} bei 223 mμ (log ε ca. 4,0) aufweist. Die C=O-Frequenz liegt im IR bei 1707–1720 cm^{-1} (NaCl) bzw. 1716–1727 (CCl_4) bzw. 1730–1732 cm^{-1} (CS_2), die C=C-Frequenz bei 1635 cm^{-1} (NaCl).

β-γ-ungesättigte bicyclische Lactone (XXIX) (XXXII) erhielten wir nur dann, wenn wir die α-Stellung durch zwei Methylgruppen blockierten. Diese entstehen durch Umsatz von *cyclo*Hexen-(1)-(α-*iso*buttersäure)-1 (XXVIII) und *cyclo*Penten-(1)-(α-*iso*buttersäure)-1 (XXXI) und zeigen erwartungsgemäss[11] eine UV-Lactonbande bei λ_{max} = 210 mμ (log ε = 3,3). Die IR-Frequenzen für C=O liegen bei 1735 cm^{-1}



(NaCl) bzw. 1736 cm^{-1} (CS_2) bezw. 1738–1740 cm^{-1} (CCl_4) und die C=C-Frequenzen bei 1655 cm^{-1} (NaCl).



* Herrn Prof. M. Pavan (Pavia) danken wir an dieser Stelle für die Ueberlassung von Iridomyrmecin sowie für den biologischen Vergleich des Iridomyrmecins mit den synthetischen Produkten.

[11] F. Korte und K. H. Löhmer, *Chem. Ber.* **91**, 1398 (1958).

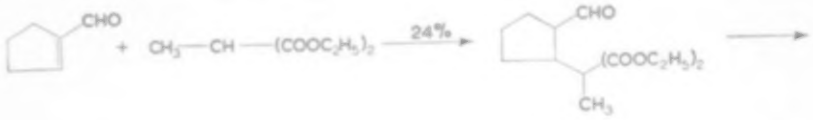
Die gleichen Absorptionen—sowohl im UV als auch im IR—findet man auch bei dem nach dem gleichen Verfahren hergestellten siebengliedrigen bicyclischen Lacton XXXVII. Aus diesem kann durch Hydrierung das gesättigte bicyclische Lacton XXXVIII dargestellt werden.

Durch diese Befunde ist gezeigt, dass sich die Prins-Reaktion gut zum Aufbau der 5-, 6- und 7-gliedrigen bicyclischen δ-Lactone anwenden lässt.

II. *Darstellung mit Hilfe der Michael-Addition*

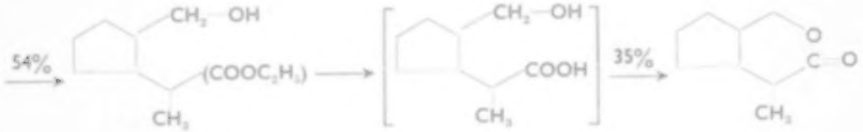
Warner und Moe war es erstmalig gelungen, eine 1:4-Addition zwischen Malonester, substituierten Malonestern oder Cyanessigester und Acrolein durchzuführen.[12]

Wir verwandten diese Methode als weitere Darstellungsmöglichkeit zur Synthese bicyclischer Lactone, indem wir von cyclischen α-β-ungesättigten Aldehyden ausgingen. So konnten Methylmalonester und *cyclo*Pentenaldehyd[13] erfolgreich der Michael-Addition unterworfen werden, wobei XXXIX entsteht.



XXXIX

Nach katalytischer Hydrierung der Aldehydgruppe erhält man den Hydroxyester (XL), der schwer rein zu erhalten ist, weil teilweise bei der Aufarbeitung schon unter Alkoholabspaltung Ringschluss zum Lacton erfolgt. Verseifung und Decarboxylierung führten zur Hydroxysäure (XLI), die jedoch nicht isoliert wurde, sondern bei der Destillation sofort in das entsprechende Lacton (XVII) überging.



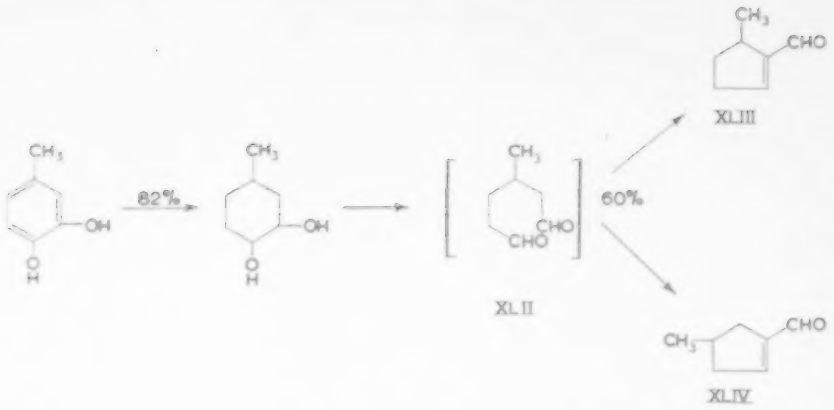
XL XLI XVII

Dieses Lacton erwies sich in seinen chemischen und physikalischen Eigenschaften, sowie dem IR-Spektrum mit dem durch die Prins-Reaktion erhaltenen Lacton (XVII) als identisch.

Um auf diesem Wege zum Iridomyrmecin zu gelangen, musste der Methyl*cyclo*pentenaldehyd (XLIII) dargestellt werden. Die Darstellung erfolgt analog der des *cyclo*Pentenaldehyds nach dem Verfahren von Brown *et al.*[13] Die katalytische Hydrierung von Homobrenzkatechin lieferte 4-Methyl-1:2-*cyclo*hexandiol, aus dem durch Glykolspaltung mit Perjodsäure der Dialdehyd XLII entsteht, der nicht isoliert, sondern gleich weiterverarbeitet wird. Durch Wasserabspaltung mit wässriger KOH können theoretisch die beiden Isomeren (XLIII) und (XLIV) gebildet werden.

[12] D. T. Warner und O. A. Moe, *J. Amer. Chem. Soc.* **70**, 2763, 3470 (1948).

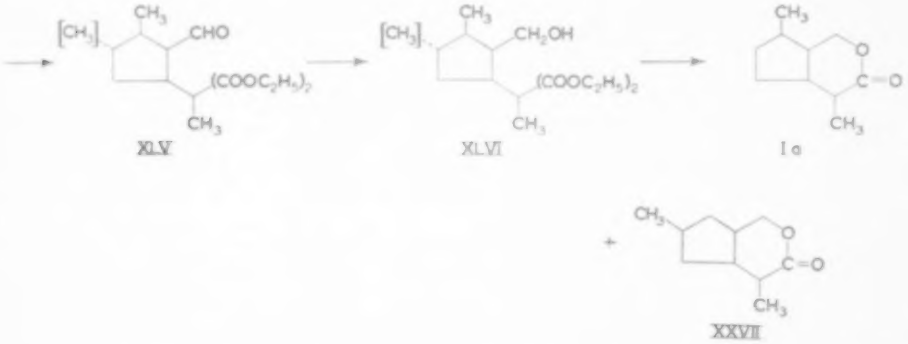
[13] J. B. Brown, H. B. Henbest und E. R. H. Jones, *J. Chem. Soc.* 3634 (1950); J. English, Jr. und G. W. Barber, *J. Amer. Chem. Soc.* **71**, 3310 (1949); E. W. Former und A. Sundralingham, *J. Chem. Soc.* 121 (1942); A. Wohl und H. Schweiger, *Ber.* **39**, 895 (1906); E. Urion, *Ann. Chim.* (11) **1**, 5 (1934).



VOL.
6
1959

Das Gaschromatogramm des Reaktionsproduktes zeigt, dass beide zu ungefähr gleichen Anteilen entstehen. (Beckman GC2, $t = 130°$, H_2-Druck 1 atü, 200 mAmp, Kolonne 17449).

Dieses Isomerengemisch wurde der Michael-Addition mit Methylmalonester unterworfen, wobei XLV entstand. Nach der Hydrierung zu XLVI liessen Verseifung, Decarboxylierung und Ringschluss daraus auf dem bereits beschriebenen Wege das Lactonisomerengemisch (Ia) und (XXXII) entstehen.

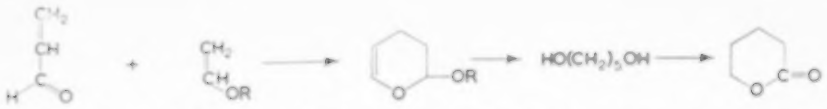


Das Isomerengemisch lässt sich gaschromatographisch auftrennen (Beckman GC2, $t = 200°$, H_2-Druck 1 atü, 200 mAmp, Kolonne 17449) und entspricht im biologischen Verhalten dem Iridomyrmecin. Die Substanz kristallisierte nicht.

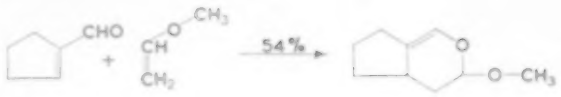
III. *Darstellung mittels Diels–Alder-Addition*

Longley und Emerson[14,15] hatten durch 1:4-Addition von Vinyläthern an α-β-ungesättigte Carbonylverbindungen substituierte 2-Alkoxy-3:4-dihydro-2H-pyrane darstellt. Durch Hydrolyse und Hydrierung wurden sie in die entsprechenden 1:5-Pentandiole überführt, die nach der Dehydrierung δ-Lactone ergaben. Es

[14] R. J. Longley Jr. und W. S. Emerson, *J. Amer. Chem. Soc.* **72**, 3079 (1950).
[15] R. J. Longley Jr. und W. S. Emerson, *J. Amer. Chem. Soc.* **74**, 2012 (1952).

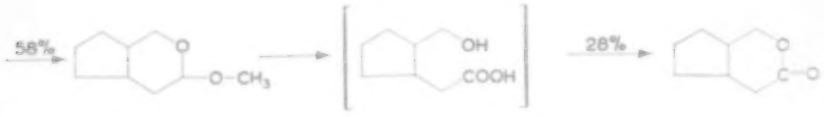


gelang uns, den *cyclo*Pentenaldehyd mit Methylvinyläther im Autoklaven bei 160° zu (XLVII) umzusetzen.



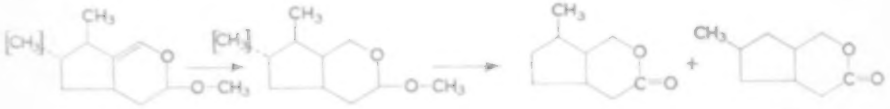
XLVII

Die Hydrierung von (XLVII) führte zu (XLVIII). Die Oxydation mit H_2O_2 im sauren Medium oder CrO_3 in Eisessig[16] führt zur Hydroxysäure (IL), die jedoch nicht isoliert wurde. Bei der Destillation der rohen Säure im Vakuum erfolgt unmittelbar der Ringschluss zum δ-Lacton (L).



XLVIII IL L

Nach dem gleichen Verfahren wurden die Lactone (LIII) und (LIV) als Isomerengemisch synthetisiert, indem als Ausgangsprodukt das Isomerengemisch (XLIII) und (XLIV) des methylsubstituierten *cyclo*Pentenaldehyds und Methyl-



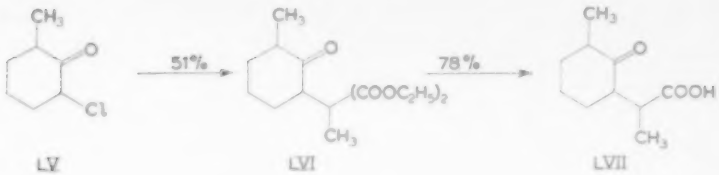
LI LII LIII LIV

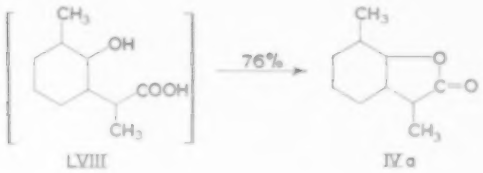
vinyläther verwandt wurden. Als Zwischenstufen erhält man LI und LII, die den Verbindungen XLVII und XLVIII analog sind.

IV. *Darstellung durch Malonestersynthese*

Zur Synthese des bicyclischen γ-Lactons IV a setzen wir 1-Methyl-3-chlor-*cyclo*hexanon-2[17] (LV) mit Methylmalonsäurediäthylester um und erhielten den disubstituierten Malonester (LVI). Anschliessende Verseifung und Decarboxylierung lieferte daraus die Säure (LVII). Die Hydrierung mit Raney-Nickel im Autoklaven liess daraus LVIII entstehen, das aber sofort zu IVa cyclisierte und nur in Form seines Natriumsalzes durch Umsatz von IV a mit NaOH in Methanol erhalten werden konnte. Die Ausbeute der Malonestersynthese beträgt bei der gebräuchlichen Arbeitsweise mit Na-Alkoholat in Alkohol nur etwa 25% d. Th., kann aber durch Arbeiten in Diäthylcarbonat als Lösungsmittel nach einer Methode von Wallniford *et al.*[18] auf 51% d. Th. verbessert werden.

[16] O. Schindler und T. Reichstein, *Helv. Chim. Acta* **39**, 1876–1891 (1956).
[17] A. Kötz und H. Steinhorst, *Liebigs Ann.* **379**, 16 (1911).
[18] V. H. Wallniford, M. A. Thorpe und A. H. Homeyer, *J. Amer. Chem. Soc.* **64**, 580 (1942).

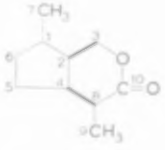




VOL. 6 1959

Sterische Betrachtungen

Für Iridomyrmecin und *iso*Iridomyrmecin kann auf Grund des Vergleichs ihrer Abbauprodukte mit den Nepetalinsäuren[19–21] eine *cis*-Stellung der Substituenten am C_2 und C_4 (Ringverknüpfung) als gesichert gelten.



Die Methylgruppe am Fünfring (C_1) steht in *trans*-Stellung zum Substituenten an C_2. Da das von uns über die Prins-Reaktion durch Animpfen mit natürlichem Iridomyrmecin erhaltene, kristalline Racemat das gleiche IR-Spektrum zeigt wie das Iridomyrmecin von Pavan, scheinen auch hier die Substituenten an C_1 und C_2 in *trans*-sowie an C_2 und C_4 in *cis*-Stellung miteinander verknüpft zu sein. Diese Annahme ist wahrscheinlich, da man *cis-trans*-Isomere am *cyclo*Pentan im Infrarot unterscheiden kann.[22] Ferner zeigt eine Betrachtung an Stuart–Briegleb–Kalotten, dass eine *cis*-Angliederung des Lactonringes an den *cyclo*Pentanring gegenüber einer *trans*-Angliederung sterisch begünstigt ist. Wir möchten daher für unser synthetisch erhaltenes Produkt den Namen D,L-Iridomyrmecin vorschlagen. Bei der Prins-Reaktion müsste dann der Formaldehydrest in *trans*-Stellung zur Methylgruppe an C_1 des *cyclo*Pentanringes eintreten, was aus sterischen Gründen verständlich ist. Bei der Hydrierung der Doppelbindung wäre zu postulieren, dass sich der Substituent an C_4 *cis* zum Substituenten an C_2 einrichtet.

Eine ähnlich eindeutige *cis*-Hydrierung wird von Conroy[23] beschrieben. Er erhält bei katalytischer Hydrierung von LIX *cis*- und mit Aluminiumamalgam *trans*-Anordnung der beiden grössten Substituenten in LX.

[19] S. M. McElvain und E. J. Eisenbraun, *J. Amer. Chem. Soc.* **77**, 1599 (1955).
[20] S. M. McElvain und E. J. Eisenbraun, *J. Org. Chem.* **22**, 976 (1957).
[21] R. B. Bates, E. J. Eisenbraun und S. M. McElvain, *J. Amer. Chem. Soc.* **80**, 3420 (1958).
[22] R. B. Bates, E. J. Eisenbraun und S. M. McElvain, *J. Amer. Chem. Soc.* **80**, 3413 (1958); *Ibid.* **80**, 3424 (1958). Verbindung Vc und Vd.
[23] H. Conroy, *J. Amer. Chem. Soc.* **74**, 3046 (1952).

Da bei der Michael-Addition von Methyl*cyclo*pentenaldehyd und Methylmalonsäurediäthylester auch nach Animpfen des Endproduktes (Ia und XXVII) mit natürlichem Iridomyrmecin keine Kristallisation erzielt werden kann, ferner das IR-Spektrum in der Feinstruktur nicht mit dem des Iridomyrmecins übereinstimmt,

ist mit einer anderen sterischen Anordnung der Substituenten an C_1, C_2 und C_4 zu rechnen. Bei Beibehaltung der nach dem Kalottenmodell günstigen *cis*-Anordnung an C_2 und C_4 kann an C_1 mit einer *cis*-Anordnung zum Substituenten C_2 gerechnet werden. Diese Annahme steht in Uebereinstimmung mit dem experimentellen Befund, dass bei Fehlen der Methylgruppe an C_1 die sowohl nach dem Prins-Reaktions—als auch dem Michael—Additionsverfahren erhaltenen Produkte (XVII) im Infrarot die gleichen Absorptionen zeigen und in allen geprüften chemischen und physikalischen Eigenschaften identisch sind.

Eine sichere Zuordnung der Konfiguration an C_1, C_2 und C_4 bei unseren synthetisch erhaltenen Produkten kann jedoch erst nach Vergleich ihrer Abbauprodukte mit den sterisch bekannten Nepetalinsäuren erfolgen.

EXPERIMENTELLER TEIL

I. *Synthesen mit Hilfe der Prins-Reaktion*

(2-*Hydroxymethyl*-cyclo*hexyl*-)-*essigsäure-lacton* (II). 55 g (2-Hydroxymethyl-*cyclo*hexyliden)-essigsäure-lacton (VI),[5] 5 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 80° und 100 atm H_2-Druck bis zur Druckkonstanz hydriert. (Dauer etwa 3 Stunden). Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt im Vak. fraktioniert destilliert. Farbloses Oel vom $Sdp_{0,01}$: 78°, Ausbeute 45 g (81% d. Th.), UV-Absorption: $\lambda_{max} = 210\ m\mu$, log $\varepsilon = 2{,}1$, IR-Carbonylbande 1730 cm^{-1} (NaCl), 1736 cm^{-1} (CCl_4). ($C_9H_{14}O_2$:(154,2) Ber. C, 70,10; H, 9,15 Gef. C, 70,58; H, 9,54%).

α-(2-*Hydroxymethyl*-cyclo*hexyliden*)-*propionsäure-lacton* (VIIIa). 154 g (1 Mol) *cyclo*Hexen-α-propionsäure, 32 g Paraformaldehyd und 500 cc Eissessig-Schwefelsäure (100 : 1,5) werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Nach dem Erkalten werden 30 g Natriumacetat zugegeben und das Lösungsmittel i.Vak. abdestilliert. Der Rückstand wird in Aether aufgenommen, mit eiskalter Sodalösung und anschliessend mit Wasser gewaschen. Nach Trocknen über Magnesiumsulfat wird der Aether abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,3}$: 97–98°, Ausbeute: 121 g (73% d. Th.), UV-Absorption: $\lambda_{max} = 223\ m\mu$, log $\varepsilon = 4{,}04$, IR-Carbonylbande 1708 cm^{-1} (NaCl), IR-C—C-Bande 1635 cm^{-1} (NaCl). ($C_{10}H_{14}O_2$: (166) Ber. C, 72,26; H, 8,49; Gef. C, 71,64; H, 8,50%)

α-(2-*Hydroxymethyl*-cyclo*hexyl*)-*propionsäure-lacton* (IXa). 100 g VIIIa, 8 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 80° und 95 atm H_2-Druck bis zur Druckkonstanz hydriert (Dauer etwa 5 Std). Dann wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das restliche Produkt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,001}$: 81–82°, Ausbeute: 85 g (84% d. Th.), UV-Absorption: $\lambda_{max} = 210\ m\mu$, log $\varepsilon = 2{,}2$, IR-Carbonylbande: 1736 cm^{-1} (CCl_4). ($C_{10}H_{16}O_2$: (168) Ber. C, 71,39; H, 9,59; Gef. C, 71,58; H, 9,56%).

α-(4-*Methyl*-2-*hydroxymethyl*-cyclo*hexyliden*)-*propionsäure-lacton*. (VIIIb). 96 g 4-Methyl-*cyclo*-Hexen-α-propionsäure, 20 g Paraformaldehyd und 250 ccm Eisessig-Schwefelsäure (100 : 1,5) werden 6 Std. lang unter Rückfluss zum Sieden erhitzt. Nach dem Erkalten werden 15 g Natriumacetat zugegeben und das Lösungsmittel abdestilliert. Der Rückstand wird in Aether aufgenommen.

VOL. 6 1959

Die ätherische Lösung wird mit eiskalter Sodalösung und dann mit Wasser gewaschen und über Magnesiumsulfat getrocknet. Nach dem Abdestillieren des Aethers wird das Reaktionsprodukt i. Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,1}$: 88°, Ausbeute : 72 g (70% d. Th.), UV-Absorption : λ_{max} = 223 mμ, log ε = 4,04, IR-Carbonylbande: 1707 cm^{-1} (NaCl), 1716 cm^{-1} (CCl_4) IR-C=C-Bande: 1635 cm^{-1} (NaCl). $C_{11}H_{16}O_2$: (180,2) Ber. C, 73,30; H, 8,95; Gef. C, 72,81; H, 9,10%.

α(4-*Methyl-2-hydroxymethyl-*cyclo*hexyl)-propionsäure-lacton* (IXb). 41 g VIIIb, 5 g Raney-Nickel und 500 ccm Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bis zur Druckkonstanz bei 95° und 100 atm. H_2-Druck hydriert. Danach wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,2}$: 92°, Ausbeute: 40 g (96% d. Th.) UV-Absorption: λ_{max} = 210 mμ, log. ε = 2,1, IR-Carbonylbande: 1735 cm^{-1} (NaCl), 1736 cm^{-1} (CCl_4). ($C_{11}H_{18}O_2$: (182,3) Ber. C, 72,49; H, 9,96; Gef. C, 72,44; H, 10,07%).

Gemisch aus α(3-*Methyl-2-hydroxymethyl-*cyclo*hexyliden)-propionsäure-lacton und* α(5-*Methyl-2-hydroxymethyl-*cyclo*hexyliden)-propionsäure-lacton* (VIII *c, d*). 70 g des Isomerengemisches aus 3-Methyl-*cyclo*hexen-α-propionsäure und 5-Methyl-*cyclo*hexen-α-propionsäure, 15 g Paraformaldehyd und 185 ccm Eisessig-Schwefelsäure(100 : 1,5)werden 6 Stunden lang unter Rückflusskühlung zum Sieden erhitzt. Nach dem Erkalten werden 11 g Natriumacetat zugegeben und das Lösungsmittel i.Vak. abdestilliert. Der Rückstand wird in Aether aufgenommen, mit eiskalter Sodalösung und anschliessend mit Wasser gewaschen und über Magnesiumsulfat getrocknet. Das nach Abdestillieren des Aethers verbleibende Produkt wird i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,1}$: 91–92°, Ausbeute: 56 g (74% d. Th.), UV-Absorption: λ_{max} = 223 mμ, log ε = 4,03, IR-Carbonylbande 1716 cm^{-1} (CCl_4), 1707 cm^{-1} (NaCl), IR-C=C-Bande: 1635 cm^{-1} (NaCl). ($C_{11}H_{16}O_2$: (180,2) Ber. C, 73,30; H, 8,95; Gef. C, 72,67; H, 9,04%).

Isomerengemisch aus α-(3-*Methyl-2-hydroxymethyl-*cyclo*hexyl)-propionsäure-lacton und* α-(5-*Methyl-2-hydroxymethyl-*cyclo*hexyl-)-propionsäure-lacton* (IX c, d). 35 g VIII c, d, 5 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 95° und 100 atm H_2-Druck bis zur Druckkonstanz hydriert. Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,2}$: 101–102°, Ausbeute: 27 g (77% d. Th.), UV-Absorption: λ_{max} = 210 mμ, log ε = 2,1, IR-Carbonylbande 1736 cm^{-1} (CCl_4). ($C_{11}H_{18}O_2$: (182,3) Ber. C, 72,49; H, 9,96; Gef. C, 72,35; H, 10,23%).

α-(2-*Hydroxymethyl-*cyclo*pentyliden)-propionsäure-lacton* (XVI). 80 g *cyclo*Penten-α-propionsäure, 20 g Paraformaldehyd und 250 cc Eisessig-Schwefelsäure (100 : 1,5) werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Nach dem Erkalten werden 15 g Natriumacetat zugegeben und das Lösungsmittel im Wasserstrahlvakuum abdestilliert. Der Rückstand wird in Aether aufgenommen und mit eiskalter Sodalösung und dann mit Wasser gewaschen. Nach Trocknen über Magnesiumsulfat wird der Aether abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,05}$: 84–85°, Ausbeute: 59,5 g (68,5% d. Th.), UV-Absorption: λ_{max} = 223 mμ, log ε = 4,01, IR-Carbonylbande 1704 cm^{-1} (NaCl), 1709 cm^{-1} (CCl_4), IR-C=C-Bande 1635 cm^{-1} (NaCl). ($C_9H_{12}O_2$: (152) Ber. C, 71,02; H, 7,95; Gef. C, 71,17; H, 8,08%).

α-(2-*Hydroxymethyl-*cyclo*pentyl)-propionsäure-lacton* (XVII). 50 g XVI, 5 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 95° und 100 atm H_2-Druck bis zur Druckkonstanz hydriert. Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt im Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,01}$: 71–72°, Ausbeute: 39,5 g (78% d. Th.), UV-Absorption: λ_{max} = 210 mμ, log ε = 2,1, IR-Carbonylbande 1753 cm^{-1} (CCl_4), 1740 cm^{-1}. (NaCl) ($C_9H_{14}O_2$: (154) Ber. C, 70,10; H, 9,15; Gef. C, 70,20; H, 9,33%).

3-*Methyl-*cyclo*pentanol*-1-(α-*propionsäureäthylester*)-1 (XVII). 120 g α-Brompropionsäureäthylester, 43 g 3-Methyl-*cyclo*pentanon-1 und 5 g Zinkspäne werden in 300 cc abs. Benzol unter Rühren auf 80° erwärmt. Sobald die Reaktion einsetzt, wird die Wärmezufuhr unterbrochen. Innerhalb von 45 Minuten werden weitere 35 g Zink portionsweise zugegeben und nach Beendigung der stürmischen Reaktion noch 3 Stunden lang unter Rückfluss zum Sieden erhitzt. Das erkaltete Reaktionsgemisch wird unter Rühren bis zur sauren Reaktion mit 20% iger H_2SO_4 versetzt. Anschliessend wird die Benzolschicht abgetrennt und die wässrige Schicht mehrfach mit Benzol ausgeschüttelt.

Die vereinigten Benzollösungen werden über $CaCl_2$ getrocknet, das Benzol abdestilliert und der Rückstand i.Vak. fraktioniert destilliert. Sdp_{20}: 122–124°, Ausbeute: 68 g (84% d. Th.).

Das Reaktionsprodukt enthält nach dem IR-Spektrum bereits etwas ungesättigten Ester. Es wird ohne weitere Reinigung weiter verarbeitet.

Isomerengemisch aus α-(3-*Methyl*-cyclo*penten*-(1)-*yl*)-*propionsäureäthylester*, α-(4-*Methyl*-cyclo*penten*-(1)-*yl*)-*propionsäureäthylester und* α(3-*Methyl*-cyclo*pentyliden*)-*propionsäureäthylester* (XIX, XX, XXI). 65 g XVIII, 18 g $POCl_3$ und 150 cc abs. Benzol werden bis zur Beendigung der HCl-Entwicklung unter Rückfluss zum Sieden erhitzt (Dauer etwa 4 Stunden). Nach dem Erkalten wird die benzolische Lösung mit Eiswasser und eiskalter Natriumbicarbonatlösung ausgeschüttelt und über $CaCl_2$ getrocknet. Nach dem Abdestillieren des Benzols wird das Produkt im Vak. fraktioniert destilliert. Farbloses Oel, Sdp_5: 97–99°, Ausbeute: 54 g (91% d. Th.), UV-Absorption: $\lambda_{max_1} = 227$ mμ, log $\varepsilon = 3{,}71$, $\lambda_{max_2} = 210$ mμ, log $\varepsilon = 3{,}27$, IR-Carbonylbanden 1707 cm^{-1} und 1735 cm^{-1} (NaCl). ($C_{11}H_{18}O_2$: (182,3) Ber. C, 72,49; H, 9,96; Gef. C, 72,21; H, 10,25%).

Nach den UV-Spektren besteht das Produkt zu 37% aus dem α-β-ungesättigten Ester XXI und zu 63% aus den β-γ-ungesättigten Estern XIX und XX.

Isomerengemisch aus α(3-*Methyl*-cyclo*penten*-(1)-*yl*)*propionsäure*, α-(4-*Methyl*-cyclo*penten*-(1)-*yl*)-*propionsäure und* α-(3-*Methyl*-cyclo*pentyliden*)-*propionsäure* (XXII, XXIII, XXIV). 51 g des Gemisches XIX, XX, XXI, 120 cc Aethanol und 30 cc 50%iger KOH werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Das erkaltete Reaktionsgemisch wird in einen Liter Wasser eingegossen und zur Entfernung der Verunreinigungen mit Aether ausgeschüttelt. Die Aetherschicht wird verworfen. Die wässrige Schicht wird mit 20%iger HCl bis zur sauren Reaktion versetzt und mit Aether mehrmals ausgeschüttelt. Die vereinigten Aetherauszüge werden über Magnesiumsulfat getrocknet, der Aether abdestilliert, und das Produkt i.Vak. fraktioniert destilliert. Dabei kann—wie die UV-Spektren zeigen—die α-β-ungesättigte Säure XXIV quantitativ abgetrennt werden.

1. *Fraktion* (XXII, XXIII): Farbloses Oel, $Sdp_{0,03}$: 70–71°, Ausbeute: 26 g (60,5% d. Th.), UV-Absorption: $\lambda_{max} = 210$ mμ, log $\varepsilon = 3{,}3$, IR-Carbonylbande 1705 cm^{-1} (NaCl). ($C_9H_{14}O_2$: (154,2) Ber. C, 70,10; H, 9,15; Gef. C, 70,04; H, 9,28%).

2. *Fraktion* (XXIV): Kristalle, Schmp. 56°, $Sdp_{0,02}$: 75–76°, Ausbeute: 14 g (32,6% d. Th.), UV-Absorption: $\lambda_{max} = 227$ mμ, log $\varepsilon = 4{,}02$, IR-Carbonylbande 1675 cm^{-1} (CCl_4). ($C_9H_{14}O_2$: (154,2) Ber. C, 70,10; H, 9,15; Gef. C, 69,72; H, 9,26%).

Isomerengemisch aus α(3-*Methyl*-2-*hydroxymethyl*-cyclo*pentyliden*)-*propionsäure*-*lacton und* α-(4-*Methyl*-2-*hydroxymethyl*-cyclo*pentyliden*)-*propionsäure*-*lacton* (XXV, XXVI). 23 g XXII, XXIII, 6,5 g Paraformaldehyd und 80 cc Eisessig-Schwefelsäure (100 : 1,5) werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Nach dem Erkalten werden 5 g Natriumacetat zugegeben und das Lösungsmittel i.Vak. abdestilliert. Der Rückstand wird in Aether aufgenommen und mit eiskalter wässriger Sodalösung und dann mit Wasser gewaschen. Nach dem Trocknen über Magnesiumsulfat wird der Aether abdestilliert. Farbloses Oel, $Sdp_{0,02}$: 70°, Ausbeute: 17 g (69% d. Th.), UV-Absorption: $\lambda_{max} = 223$ mμ, log $\varepsilon = 4{,}0$, IR-Carbonylbande 1710 cm^{-1}, IR-C=C-Bande 1635 cm^{-1} (NaCl) ($C_{10}H_{14}O_2$: (166,2) Ber. C, 72,26; H, 8,49; Gef. C, 72,16; H, 8,55%).

D,L-*Iridomyrmecin* (Ia). 9 g XXV, XXVI, 3 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 100° und 100 atm H_2-Druck bis zur Druckkonstanz hydriert. (Dauer etwa zwei Stunden). Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. $Sdp_{0,3}$: 82°, Ausbeute: 7,5 g (83% d. Th.).

Aus dem farblosen Oel kristallisieren nach Zugabe eines Impfkristalles (Prof. M. Pavan) im Kühlschrank bei −3° 3,5 g Iridomyrmecin aus. Die Kristalle werden viermal aus Petroläther umkristallisiert. Lange Nadeln, Schmp: 59°, UV-Absorption: $\lambda_{max} = 210$ mμ. log $\varepsilon = 2{,}1$, IR-Carbonylbande 1753 cm^{-1} (CCl_4), die Substanz ist optisch inaktiv. ($C_{10}H_{16}O_2$: (168,2) Ber. C, 71,39; H, 9,59; O, 19,02; MW, 168,2; Gef. C, 71,18; H, 9,75; O, 19,25; MW, 181).

Lactontitration: *n*/10 HCl Ber. 8,1 cc; Gef. 8,1 cc.

α-(2-*Hydroxymethyl*-cyclo*hexen*-(1)-*yl*)-iso*buttersäure*-*lacton* (XXIX). 37 g *cyclo*Hexen-α-*iso*-buttersäure, 8 g Paraformaldehyd und 100 cc Eisessig-Schwefelsäure (100 : 1,5) werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Nach dem Erkalten werden 6 g Natriumacetat zugegeben und das Lösungsmittel abdestilliert. Der Rückstand wird mit Aether aufgenommen, mit eiskalter Sodalösung und dann mit Wasser gewaschen und über Magnesiumsulfat getrocknet. Nach dem Abdestillieren des Aethers wird das Reaktionsprodukt im Hochvakuum fraktioniert destilliert.

Farbloses Oel, $Sdp_{0,5}$: 82–83°, Ausbeute: 31 g (82% d. Th.), UV-Absorption: λ_{max} = 209,5 mμ, log ε = 3,2, IR-Carbonylbande: 1735 cm^{-1} (NaCl), 1736 cm^{-1} (CS_2), 1740 cm^{-1} (CCl_4), IR-C=C-Bande: 1657 cm^{-1} (NaCl), 1655 cm^{-1} (CS_2), 1655 cm^{-1} (CCl_4). ($C_{11}H_{16}O_2$: (180,2) Ber. C, 73,30; H, 8,95; Gef. C, 73,34; H, 9,16%).

α(2-*Hydroxymethyl*-cyclo*hexyl*)-iso*buttersäure-lacton* (XXX). 20 g XXIX, 4 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 95° und 100 atm H_2-Druck bis zur Druckkonstanz hydriert (Dauer etwa 3 Stunden). Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,4}$: 85°, Ausbeute: 19 g (94% d. Th.), UV-Absorption: λ_{max} = 210 mμ, log ε = 2,1, IR-Carbonylbande: 1736 cm^{-1} (CCl_4). ($C_{11}H_{18}O_2$: (182,3) Ber. C, 72,49; H, 9,96; O, 17,56; MW, 182,3; Gef. C, 72,74; H, 10,21; O, 17,29; MW, 184).

α-(2-*Hydroxymethyl*-cyclo*penten*-(1)-*yl*)-iso*buttersäure-lacton* (XXXII). 52 g *cyclo*Penten-α-*iso*-buttersäure, 12,5 g Paraformaldehyd und 150 cc Eisessig-Schwefelsäure (100 : 1,5) werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Nach dem Erkalten werden 10 g Natriumacetat zugegeben und das Lösungsmittel i.Vak. abdestilliert. Der Rückstand wird mit Aether aufgenommen, mit eiskalter Sodalösung und dann mit Wasser gewaschen. Nach dem Trocknen über Magnesiumsulfat wird der Aether abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,01}$: 58–60°, Ausbeute: 45 g (80% d. Th.), UV-Absorption: λ_{max} = 210 mμ, log ε = 3,3, IR-Carbonylbande 1735 cm^{-1} (NaCl), 1738 cm^{-1} (CCl_4). ($C_{10}H_{14}O_2$: (166,2) Ber. C, 72,26; H, 8,49; Gef. C, 71,80; H, 8,65%).

α(2-*Hydroxymethyl*-cyclo*pentyl*)-iso*buttersäure-lacton* (XXXIII). 23 g XXXII, 3 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 95° und 100 atm H_2-Druck bis zur Druckkonstanz hydriert. Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,2}$: 81–82°, Ausbeute: 20 g (80% d. Th.), UV-Absorption: λ_{max} = 210 mμ, log ε = 2,1, IR-Carbonylbande 1736 cm^{-1} (NaCl). ($C_{10}H_{16}O_2$: (168,2) Ber. C, 71,39; H, 9,59; Gef. C, 71,07; H, 9,47%).

cyclo*Heptanol*-1-(α-iso*buttersäureäthylester*)-1 (XXXIV). 250 g α-Brom*iso*buttersäureäthylester, 128 g *cyclo*Heptanon, 8 g Zinkspäne und eine Spur Jod werden in 600 cc abs. Benzol unter Rühren auf 80° erwärmt. Sobald die Reaktion einsetzt, wird die Wärmezufuhr unterbrochen. Innerhalb einer Stunde werden noch weitere 75 g Zinkspäne portionsweise zugegeben. Nach Beendigung der stürmischen Reaktion wird unter Rühren noch 3 Stunden unter Rückfluss zum Sieden erhitzt. Das erkaltete Reaktionsgemisch wird bis zur sauren Reaktion unter Rühren mit eiskalter 20%iger Schwefelsäure versetzt. Anschliessend wird die Benzolschicht abgetrennt und die wässrige Schicht mehrmals mit Benzol ausgeschüttelt. Die vereinigten Benzolschichten werden über $CaCl_2$ getrocknet, das Benzol abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Sdp_9: 132–133°, Ausbeute 189 g (83% d. Th.). Das Reaktionsprodukt enthält nach den I.R.-Spektren bereits etwas ungesättigten Ester XXXV. Es wird ohne weitere Reinigung weiterverarbeitet.

α-(cyclo*Hepten*-(1)-*yl*)-iso*buttersäureäthylester* (XXXV). 145 g XXXIV werden zusammen mit 300 g $KHSO_4$ 3 Stunden lang unter Rückfluss auf 130–140° erhitzt. Nach dem Erkalten wird der Kolbeninhalt bis zur völligen Lösung des $KHSO_4$ mit Wasser versetzt. Das abgeschiedene Oel wird in Aether aufgenommen und die wässrige Schicht mehrmals mit Aether ausgeschüttelt. Die vereinigten Aetherauszüge werden über Magnesiumsulfat getrocknet, der Aether abdestilliert und das verbleibende Produkt i.Vak. fraktioniert destilliert. Farbloses Oel, Sdp_{10}: 121–122°, Ausbeute: 111 g (86,5% d. Th.), UV-Absorption: λ_{max} = 210 mμ, log ε = 3,3, IR-Carbonylbande 1725 cm^{-1} (NaCl). ($C_{12}H_{22}O_2$: (210,3) Ber. C, 74,24; H, 10,54; Gef. C, 74,40; H, 10,33%).

α(cyclo*Hepten*-(1)-*yl*)-iso*buttersäure* (XXXVI). 100 g XXXV, 200 cc Aethanol und 50 cc 50%ige KOH werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Das erkaltete Reaktionsgemisch wird in 1,5 l. Wasser eingegossen und zur Entfernung der Verunreinigungen mit Aether ausgeschüttelt. Die Aetherschicht wird verworfen. Die wässrige Schicht wird bis zur sauren Reaktion mit 20%iger HCl versetzt, und mit Aether ausgeschüttelt. Die vereinigten Aetherauszüge werden über Magnesiumsulfat getrocknet, der Aether abdestilliert und das zurückbleibende kristalline Produkt aus Petroläther umkristallisiert. Blättchen, Schmp: 82°, Ausbeute: 78 g (82,1% d. Th.), UV-Absorption: λ_{max} = 210 mμ, log ε = 3,3, IR-Carbonylbande 1700 cm^{-1} (CCl_4). ($C_{11}H_{18}O_2$: (182,3) Ber. C, 72,49; H, 9,96; O, 17,56; Gef. C, 72,23; H, 10,23; O, 17,49%).

α(2-*Hydroxymethyl*-cyclo*hepten*-(1)-*yl*)-iso*buttersäure-lacton* (XXXVII). 35 g XXXVI, 7 g

Paraformaldehyd und 100 cc Eisessig-Schwefelsäure (100 : 1,5) werden 6 Stunden lang unter Rückfluss zum Sieden erhitzt. Nach dem Erkalten werden 6 g Natriumacetat zugegeben und das Lösungsmittel im Vak. abdestilliert. Der Rückstand wird in Aether aufgenommen und mit eiskalter Sodalösung und dann mit Wasser ausgeschüttelt. Nach dem Trocknen über Magnesiumsulfat wird der Aether abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,1}$: 90–91°, Ausbeute: 29 g (79% d. Th.), UV-Absorption: $\lambda_{max} = 210$ mμ, $\log \varepsilon = 3{,}3$, IR-Carbonylbande 1735 cm^{-1} (NaCl). ($C_{12}H_{18}O_2$: (194,3) Ber. C, 74,19; H, 9,34; Gef. C, 73,78; H, 9,62%).

α-(2-*Hydroxymethyl*-cyclo*heptyl*)-*isobuttersäure-lacton* (XXXVIII). 21 g XXXVII, 4 g Raney-Nickel und 500 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 95° und 100 atm H_2-Druck bis zur Druckkonstanz hydriert. Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,03}$: 80°, Ausbeute: 20 g (94,5% d. Th.), UV-Absorption: $\lambda_{max} = 210$ mμ, $\log \varepsilon = 2{,}1$, IR-Carbonylbande 1736 cm^{-1} (NaCl), 1740 cm^{-1} (CCl_4). ($C_{12}H_{20}O_2$: (196,3) Ber. C, 73,43; H, 10,27; Gef. C, 73,33; H, 10,51%).

Versuche zur Michael-Addition

Methyl-(2-*formyl*-cyclo*pentyl*)-*malonsäurediäthylester* (XXXIX). Zu 200 cc abs. Alkohol werden 0,04 g Natrium gegeben. Dazu tropft man 63 g frisch destillierten Methylmalonsäurediäthylester. Man kühlt die Mischung auf 0° und gibt unter Rühren 37 g *cyclo*Pentenaldehyd zu. Es wird noch 2 Stunden gerührt und über Nacht im Kühlschrank stehen gelassen. Nach Neutralisation mit Eisessig wird der Alkohol i.Vak. abdestilliert, mit 200 cc Benzol aufgenommen und mit 2 mal 50 cc Wasser gewaschen. Nach Trocknen über Na_2SO_4 und Abdestillieren des Lösungsmittels wird i. Hochvak. fraktioniert. Farbloses Oel vom $Sdp_{0,2}$: 102°, Ausbeute: 24% d. Th., UV-Absorption: $\lambda_{max} = 211$ mμ, $\log \varepsilon = 2{,}44$, IR-Carbonylbande 1725 cm^{-1} (NaCl). ($C_{14}H_{22}O_5$: (270,3) Ber. C, 62,20; H, 8,20; Gef. C, 62,44; H, 8,59%).

Das 2:4-Dinitrophenylhydrazon hat einem Schmp = 104,5–105,5°, umkristallisiert aus Aethanol, gelbe Nädelchen. ($C_{20}H_{26}O_8N_4$: (450,4) Ber. C, 53,33; H, 5,82; N, 12,44; Gef. C, 53,63; H, 5,85; N, 12,23%).

Methyl-(2-*hydroxymethyl*-cyclo*pentyl*)-*malonsäurediäthylester* (XL). 66 g XXXIX werden in 300 cc abs. Alkohol mit 15 g Raney-Nickel unter Zusatz einer kleinen Menge NaOH im Rührautoklaven bei 150° und 125 atm H_2-Druck 6 Stunden lang hydriert. Die Fraktionierung liefert XL als farbloses Oel mit einem $Sdp_{0,4} = 125°$, Ausbeute: 59% d. Th., UV-Absorption: $\lambda_{max} = 211$ mμ, $\log \varepsilon = 2{,}37$, IR-Carbonylbande bei 1725 cm^{-1} (NaCl), IR-OH-Bande bei 3420 cm^{-1} (NaCl). ($C_{14}H_{24}O_5$: (272,3) Ber. C, 61,74; H, 8,88,; Gef. C, 61,37; H, 8,60%).

α-(2-*Hydroxymethyl*-cyclo*pentyl*)-*propionsäure-lacton* (XVII). 25 g XL werden mit 30 g KOH in 105 cc Methanol 7 Stunden lang unter Rückfluss erhitzt und anschliessend noch 10 Stunden bei Zimmertemperatur gerührt. Dann wird der grösste Teil des Methanols abdestilliert, der Rückstand mit Wasser versetzt, mit Aether zur Beseitigung von noch nicht verseiftem Ester ausgeschüttelt, mit HCl unter Kühlung angesäuert und erneut mit Aether ausgeschüttelt. Das nach dem Abdestillieren des Aethers verbleibende Oel wird mit 20 cc 2 N H_2SO_4 3 Stunden lang in einem Oelbad auf 115° erhitzt, ausgeäthert, getrocknet und fraktioniert. Farbloses Oel vom $Sdp_{0,2} = 70–71°$, Aubeute: 35% d. Th., UV-Absorption: $\lambda_{max} = 210$ mμ, $\log \varepsilon = 2{,}12$, IR-Carbonylbande bei 1753 cm^{-1} (CCl_4), 1735 cm^{-1} (NaCl). ($C_9H_{14}O_2$: (154,2) Ber. C, 70,10; H, 9,15; Gef. C, 69,81; H, 9,23%).

5-*Methyl*-cyclo*penten*-(1)-*aldehyd*-1 *und* 4-*Methyl*-cyclo*penten*-(1)-*aldehyd*-1 *als Isomerengemisch.* (XLIII) und (XLIV). In 1,8 l. Wasser werden 150 g $NaJO_4$ suspendiert, 35 cc konz. HNO_3 zugefügt und bis zum Lösen gerührt. Mit wässriger NaOH wird die Lösung auf pH 4 gebracht. Dann werden 80 g 4-Methyl-1:2 *cyclo*hexandiol langsam zugegeben. Dabei steigt die Temperatur von 18° auf 30°. Es wird 20 Minuten gerührt und auf 25° abgekühlt. Dann gibt man 250 cc Aether hinzu und 210 cc einer 20%igen KOH-Lösung. Es wird noch 30 Minuten stark gerührt, die Aetherschicht abgetrennt, die wässrige Phase mit fünfmal 200 cc Aether ausgeschüttelt und die vereinigten Aetherauszüge über Na_2SO_4 getrocknet. Bei der Destillation erhält man XLIII und XLIV als farbloses Flüssigkeitsgemisch von benzaldehydartigem Geruch. $Sdp_{12} = 49–51°$, Ausbeute: 60% d. Th. UV-Absorption: $\lambda_{max} = 235$ mμ, $\log \varepsilon = 4{,}02$, IR-Carbonylbande bei 1680 cm^{-1} (NaCl), IR-C=C-Bande bei 1614 cm^{-1} (NaCl). ($C_7H_{10}O$: (110,2) Ber. C, 76,32; H, 9,15; Gef. C, 75,17; H, 9,02%).

Das 2:4-Dinitrophenylhydrazon kristallisiert aus Aethanol in orangegelben Nädelchen. Schmp.

160–165°. ($C_{13}H_{14}O_4N_4$: (290,27) Ber. C, 53,79; H, 4,86; N, 19,30; Gef. C, 53,12; H, 4,75; N, 19,77%).

Isomerengemisch aus Methyl-(3-Methyl-2-formyl-cyclopentyl)-malonsäurediäthylester) und Methyl-(4-Methyl-2-formyl-cyclopentyl)-malonsäurediäthylester (XLV). Die Darstellung erfolgt analog der von XXXIX. Ausgehend von 40 g des Gemisches XLIII und XLIV und 65 g Methylmalonsäurediäthylester erhält man bei der Aufarbeitung (XLV) als farbloses Oel vom $Sdp_{0,3}$ = 106°. Ausbeute 24% d. Th., UV-Absorption: λ_{max} = 211 mμ, log ε = 2,48, IR-Carbonylbande bei 1725 cm^{-1} (NaCl). ($C_{13}H_{24}O_6$: (284,3) Ber. C, 63,36; H, 8,15; Gef. C, 62,55; H, 8,74%).

Das 2:4-Dinitrophenylhydrazon kristallisiert in goldgelben Nädelchen und hat einen Schmp = 145,5–146,5°. Umkristallisiert aus Aethanol. ($C_{21}H_{28}O_8N_4$: (467,5) Ber. C, 54,30; H, 6,08; N, 12,06; Gef. C, 53,49; H, 5,93; N, 12,31%).

Isomerengemisch aus Methyl-(3-Methyl-2-hydroxymethyl-cyclopentyl)-malonsäurediäthylester und Methyl-(4-Methyl-2-hydroxymethyl-cyclopentyl)-malonsäurediäthylester. (XLVI). Die Darstellung erfolgt analog der von XL. Das durch Hydrierung von (XLV) erhaltene Isomerengemisch ist ein farbloses Oel und hat einem $Sdp_{0,2}$ = 114°. Ausbeute: 56% d. Th., UV-Absorption λ_{max} = 211 mμ, log ε = 2,43, IR-Carbonylbande bei 1725 cm^{-1} (NaCl), IR-OH-Bande bei 3400 cm^{-1} (NaCl). ($C_{13}H_{26}O_5$: (286,4) Ber. C, 62,91; H, 9,15; Gef. C, 63,85; H, 10,33%).

Bei der Destillation erfolgt teilweise Alkoholabspaltung zum Lacton.

Gemisch aus α-(3-Methyl-2-hydroxymethyl-cyclopentyl)-propionsäure-lacton (Ia) *und α-(4-Methyl-2-hydroxymethyl-cyclopentyl)-propionsäure-lacton* (XXVII). Die Darstellung erfolgt im wesentlichen analog der von (XVII). Nach der Verseifung von (XLVI) mit methanolischer KOH wird die Decarboxylierung ohne Zusatz von Säure durch vierstündiges Erhitzen auf 120° durchgeführt. Bei der Fraktionierung erhält man ein farbloses Oel vom $Sdp_{0,1}$ = 71–73°. Ausbeute: 42% d. Th., UV-Absorption: λ_{max} = 210 mμ, log ε = 2,14, IR-Carbonylbande bei 1753 cm^{-1} (CCl_4), 1740 cm^{-1} (NaCl). ($C_{12}H_{18}O_2$: (168,2) Ber. C, 71,39; H, 9,59; Gef. C, 71,11; H, 9,84%).

Versuche zur Diels–Alder Addition

3-Methoxy-3:4:4a: 5:6:7-hexahydro-cyclopenta (c) pyran (XLVII). 63 g Methylvinyläther, 80 g *cyclo*Pentenaldehyd und 0,2 g Hydrochinon werden im Autoklaven 12 Stunden lang bei 160° unter einer Stickstoffatmosphäre gerührt. Das Reaktionsgemisch wird im Vakuum fraktioniert und liefert XLVII als farblose Flüssigkeit, die sich beim längeren Stehen verfärbt. Sdp_{12} = 83–86°, Ausbeute: 59% der Theorie, UV-Absorption: λ_{max} = 211 mμ, log ε = 3,65, IR-C=C-Bande bei 1677 cm^{-1} (NaCl). ($C_8H_{14}O_2$: (154,2) Ber. C, 70,10; H, 9,15; Gef. C, 70,85; H, 9,41%).

3-Methoxy-octahydro-cyclopenta (c) pyran (XLVIII). 16 g XLVII werden in 300 cc abs. Alkohol mit 10 g Raney-Nickel 3 Stunden lang im Autoklaven bei 125° und 85 atm H_2-Druck hydriert. Die Fraktionierung ergibt XLVIII als farblose Flüssigkeit mit einem Sdp_{10} = 78°. Ausbeute: 58% der Theorie. Die Substanz zeigt keine UV-Absorption zwischen 180 und 360 mμ. ($C_8H_{16}O_2$: (156,2) Ber. C, 69,19; H, 10,32; Gef. C, 68,92; H, 10,39%).

(2-Hydroxymethyl-cyclopentyl)-essigsäure-lacton (L). 7 g XLVIII werden mit 10 cc 2 N H_2SO_4 und 5 cc Wasser 6 Stunden lang bei 50° gerührt. Dann wird mit $NaHCO_3$ auf pH 6 gebracht. Nach Rühren über Nacht gibt man 12 cc 15%iges H_2O_2 hinzu und erwärmt 4 Stunden lang auf 50°. Nach Ausäthern und Trocknen des Aethers erhält man L bei der Fraktionierung mit einem Sdp_{10} von 134–136° in 28%iger Ausbeute. UV-Absorption: λ_{max} = 210,5 mμ, log ε = 2,02, IR-Carbonylbande bei 1753 cm^{-1} (CCl_4), 1740 cm^{-1} (NaCl). ($C_8H_{12}O_2$: (140,2) Ber. C, 68,54; H, 8,63; Gef. C, 68,16; H, 8,85%).

Gemisch aus 6-Methyl-3-methoxy-3:4:4a:5:6:7-hexahydro-cyclopenta (c)-pyran und 7-Methyl-3-methoxy-3:4:4a:5:6:7-hexahydrocyclopenta (c)-pyran. (LI). 140 g des Gemisches XLIII und XLIV sowie 116 g Methylvinyläther werden unter Zusatz von 0,2 g Hydrochinon 12 Stunden lang im Rührautoklaven bei 175° unter 20 atm N_2-Druck gehalten. Durch Fraktionierung i.Vak. erhält man das Isomerengemisch (LI) als farblose Flüssigkeit vom Sdp_{10} = 83°. Ausbeute: 33% d. Th., UV-Absorption: λ_{max} = 211 mμ, log ε = 3,67, IR-C=C-Bande bei 1677 cm^{-1} (NaCl). ($C_{10}H_{16}O_2$: (168,2) Ber. C, 71,39; H, 9,59; Gef. C, 70,61; H, 9,74%).

Gemisch aus 6-Methyl-3-methoxy-octahydro-cyclopenta-(c)-pyran und 7-Methyl-3-methoxy-octahydro-cyclopenta (c) pyran. (LII). 24 g (LI) werden im Rührautoklaven mit 10 g Raney-Nickel in abs. Alkohol bei 125° und 85 atm H_2-Druck 3 Stunden lang hydriert. Die fraktionierte Destillation ergibt das Isomerengemisch (LII). Sdp_{10} = 83–85°, Ausbeute: 67% d. Th., Die Substanz zeigt

keine UV-Absorption zwischen 180 und 360 mμ. ($C_{10}H_{16}O_2$: (170,2) Ber. C, 70,54; H, 10,66; Gef. C, 70,88; H, 10,75%).

Isomerengemisch aus (3-Methyl-2-hydroxymethyl-cyclopentyl)-essigsäure-lacton (LIII) *und (4-Methyl-2-hydroxymethyl-cyclopentyl)-essigsäure-lacton* (LIV). 17 g des Isomerengemisches (LII) werden in 50 cc Eisessig gelöst und mit 10 g CrO_3 in 500 cc Eisessig versetzt. Es tritt Erwärmung und Farbumschlag nach grün ein. Nach 3 Stunden wird der Eisessig i.Vak. abdestilliert, der Rückstand mit Wasser aufgenommen, mit Aether dreimal ausgeschüttelt. Der Aether wird zweimal mit 2 n H_2SO_4 und zweimal mit Wasser gewaschen, getrocknet und abdestilliert. Das Lactongemisch siedet bei einem Sdp_{16} = 137–140°. Ausbeute: 23% d. Th., UV-Absorption: λ_{max} = 210 mμ, log ε = 2,1, IR-Carbonylbande bei 1753 cm^{-1} (CCl_4), 1743 cm^{-1} (NaCl). ($C_9H_{14}O_2$: (154,2) Ber. C, 70,10; H, 9,15; Gef. C, 69,61; H, 9,03%).

Versuche zur Malonester synthese

2-Oxo-3-methyl-cyclohexan-(methylmalonsäure)-(1)-diäthylester (LVI). 23 g Natrium werden in 250 cc abs. Aethanol gelöst und das überschüssige Aethanol i.Vak. abdestilliert. Dann werden zuerst 100 g Diäthylcarbonat und darauf 174 g Methylmalonsäurediäthylester zugetropft. Nach zweistündigem Erwärmen auf 80° wird das gebildete Aethanol i.Vak. abdestilliert. Dann werden langsam 150 g Chlormethylcyclohexanon (LV) in 200 cc Diäthylcarbonat zugetropft, wobei sich der Kolbeninhalt stark erwärmt und NaCl ausfällt. Es wird noch 5 Stunden lang auf 90° erwärmt und dann in Eiswasser eingegossen. Nach dem Lösen des NaCl werden die beiden auftretenden Schichten getrennt und die wässrige Schicht mit Aether ausgeschüttelt. Die mit dem Oel vereinigten Aetherschichten werden über Magnesiumsulfat getrocknet, der Aether und das Diäthylcarbonat abdestilliert und das Produkt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,03}$: 116–120°, Ausbeute: 145 g (51,1% d. Th.), IR-Carbonylbande 1745 cm^{-1} (NaCl). ($C_{15}H_{24}O_5$: (284,3) Ber. C, 63,36; H, 8,51; Gef. C, 63,44; H, 8,38%).

2-Oxo-3-methyl-cyclohexan-(α-propionsäure)-(1) (LVII). 100 g KOH, 120 cc H_2O und 142 g LVI werden unter Rühren 5 Stunden lang am Rückfluss zum Sieden erhitzt. Dann werden 200 cc H_2O zugegeben und der gebildete Alkohol abdestilliert. Unter Eiskühlung werden dann langsam 190 g konz. H_2SO_4 in 200 cc H_2O zugetropft. Es wird bis zur Beendigung der CO_2-Entwicklung auf 100° erwärmt (Dauer etwa 3 Stunden). Das gebildete Oel wird in Aether aufgenommen und die wässrige Schicht mit Aether ausgeschüttelt. Die vereinigten Aetherlösungen werden über Magnesiumsulfat getrocknet, der Aether abdestilliert und das Reaktionsprodukt im Vakuum fraktioniert destilliert. Hochviskoses Oel, $Sdp_{0,02}$: 111–113°, Ausbeute: 74 g (78,4% d. Th.). ($C_{10}H_{16}O_3$: (184,2) Ber. C, 65,19; H, 8,75; Gef. C, 65,18; H, 8,74%).

Lacton der 2-Methyl-cyclohexanol-1-(α-propionsäure)-6 (IVa). 184 g LVII, 20 g Raney-Nickel und 300 cc Aethanol werden in einen Druckrührautoklaven gebracht. Es wird bei 120° und 130 atm H_2-Druck bis zur Druckkonstanz hydriert. Anschliessend wird vom Raney-Nickel abfiltriert, das Lösungsmittel abdestilliert, und das Reaktionsprodukt i.Vak. fraktioniert destilliert. Farbloses Oel, $Sdp_{0,01}$: 77–78°, Ausbeute: 128 g (76,2% d. Th.), UV-Absorption: λ_{max} = 211 mμ, log ε = 2,4, IR-Carbonylbande 1772 cm^{-1}, (NaCl). ($C_{10}H_{16}O_2$: (168,2) Ber. C, 71,39; H, 9,59; Gef. C, 71,06; H, 9,54%).

Die IR-Spektren wurden mit dem Perkin–Elmer Modell 21 gemessen, entweder gelöst in organischen Lösungsmitteln gegen diese Lösungsmittel (CCl_4) und (CS_2) oder als Oel zwischen NaCl-Scheiben gegen Luft (NaCl). Alle UV-Spektren wurden in Methanol mit dem Beckman DKI gemessen. Die Schmelzpunkte sind unkorrigiert.

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VOL.
6
1959

SYNTHESIS OF D- AND L-*ISO*IRIDOMYRMECIN AND RELATED COMPOUNDS

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(*Received* 12 *December* 1958)

Abstract—Starting from D-citronellal of natural origin, D-iridodial and D-*iso*iridomyrmecin were synthesised.* The latter furnished, on oxidation, a *nepetalinic acid*, which was the enantiomorph of a degradation product of nepetalactone. A mixture of the two specimens afforded a *racemate* of higher melting point.

L-Citronellal, obtained (Boake, Roberts & Co.) by a series of chemical transformations from pinene was similarly converted into L-iridodial and L-*iso*iridomyrmecin. The latter was identical with the natural product from *Iridomyrmex nitidus*.

INSPECTION of the structure (I) of iridomyrmecin[1,2] and related compounds[3,4] isolated from different species of ants of the genus *Iridomyrmex* suggested a biogenesis by disproportionation of the dialdehyde (II), which, known as iridodial, has been isolated from *I. conifer* and *I. detectus* and actually converted into *iso*iridomyrmecin, epimeric with (I) at the asterisked C-atom. It is accordingly probable that iridodial is the biological precursor both of (I) and its epimer.

Going back a stage further in the analysis it was evident that iridodial could be regarded as a cyclised oxo-citronellal (=CMe_2 → =CMeCHO), the ring-formation being of a normal Michael reaction type as exemplified by the addition of phenylacetaldehyde to acrolein:—

The oxidation itself was thought a plausible process in view of the activation of terminal methyl by the neighbouring double bond.

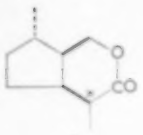
The syntheses now described represent the realisation of this biogenetic scheme in the laboratory.

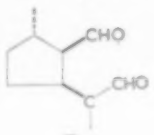
The structure (I)† proposed for iridomyrmecin,[2] and later for its epimer *iso*-iridomyrmecin[4,5] appears to be firmly established except that the configuration at the asterisked C-atom has not yet been defined.

* U.K. Patent Application No. 18220/57.
† The recently revised steric formulae[6,7] are used for this and related compounds.

[1] M. Pavan, *Chim. e Industr.* **37**, 625 (1955).
[2] R. Fusco, R. Trave and A. Vercellone, *Chim. e Industr.* **37**, 251, 958 (1955).
[3] G. W. K. Cavill, D. L. Ford and H. D. Locksley, *Chem. & Ind.* 465 (1956); *Austr. J. Chem.* **9**, 288 (1956).
[4] G. W. K. Cavill and H. D. Locksley, *Austr. J. Chem.* **10**, 352 (1957).
[5] S. M. McElvain and E. J. Eisenbraun, *J. Org. Chem.* **22**, 976 (1957).

The iridolactones* have been oxidised to two epimeric nepetalinic acids[6-8] (III) and thus are related to nepetalactone (IV), a constituent of catnip oil.[6-9] In order to realise the above scheme of synthesis we started from the more readily accessible


I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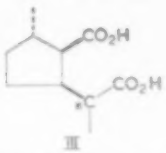
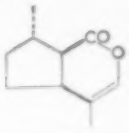
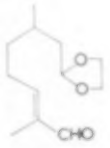

III

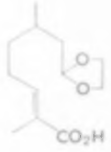

IV

D-citronellal. Its ethylene acetal (V)† was oxidised by means of selenium dioxide in ethanol to the $\alpha\beta$-unsaturated aldehyde (VI). There was no evidence of the formation of the isomeric ketone (VII). A similar oxidation could not be effected with citronellal diethyl acetal, the starting material being recovered virtually quantitatively. After isolation of the product (VI) by means of the bisulphite addition compound its infra-red spectrum showed the characteristic stretching frequency of an aldehydic C—H bond at 3·70 μ and had bands at 5·92 and 6·10 μ for a conjugated carbonyl group and double bond, respectively. Further evidence for the constitution of (VI) was provided by almost quantitative oxidation with alkaline silver oxide to the corresponding acid (VIII).

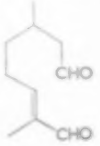
V†

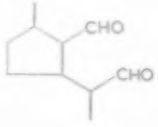

VI

VII


VIII

It was anticipated that acid hydrolysis of the aldehydo-acetal (VI) would yield the aliphatic dialdehyde (IX), but examination of various conditions soon revealed that, in addition, the alicyclic dialdehyde (X) was formed in acid media. Thus carefully controlled hydrolysis of the aldehydo-acetal (VI) with 50 per cent aqueous acetic acid in an inert atmosphere consistently produced the two isomeric dialdehydes


IX


X

(IX) and (X) in approximately equal quantities; the products were readily separated by fractional distillation and their infra-red spectra were in agreement with the structures assigned to them. The two dialdehydes readily polymerised and also formed acidic material in contact with air. Hence they tended to give low carbon values on analysis.

* The term iridolactones is used to cover both iridomyrmecin and *iso*iridomyrmecin.

† Formulae (V), (VI), (IX) and (X) are used for both D- and L-isomers.

[6] S. M. McElvain and E. J. Eisenbraun, *J. Amer. Chem. Soc.* **77**, 1955 (1955).

[7] E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.* **77**, 3383 (1955).

[8] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.* **80**, 3420 (1958).

[9] S. M. McElvain, R. D. Bright and P. R. Johnson, *J. Amer. Chem. Soc.* **63**, 1558 (1941); J. Meinwald, *Ibid.* **76**, 4571 (1954).

The compounds (IX) and (X) were characterised as the bis-2:4-dinitrophenylhydrazones and bis-semicarbazones; the derivatives of the cyclic dialdehyde (X) had the same melting points as those reported for the corresponding derivatives of natural iridodial[3] and were undepressed on admixture with authentic samples, kindly provided by Dr. G. W. K. Cavill.

Attempts to increase the yield of the cyclic dial (X) at the expense of the aliphatic isomer (IX) by prolonging the treatment with aqueous acetic acid remained unsuccessful. We found, however, that cyclisation of the dialdehyde (IX) could be achieved by refluxing this substance with acetone containing some dilute hydrochloric acid; thus iridodial (X) was obtained in up to 50 per cent yield, but the remainder of the material polymerized under these conditions.

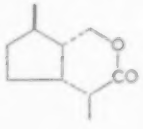
VOL. 6 1959

Contrary to expectations the aliphatic dialdehyde (IX) failed to cyclise in the presence of mild basic reagents (e.g. piperidine).[10] Treatment with sodium methoxide in methanol and subsequent acidification produced a neutral, sweetly smelling liquid which analysed for the empirical formula $C_{10}H_{16}O_2$ and had a band in the carbonyl region at 5·76 μ, indicating that the substance was a δ-lactone.

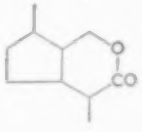
A portion of this material was oxidised with alkaline permanganate and the resulting mixture of acids was separated by means of their barium salts. The soluble salts furnished a di-basic acid, m.p. 142–143° $[\alpha]_D^{28}$ −16° which analysed for the empirical formula $C_{10}H_{16}O_4$ and formed a bis-*p*-bromphenacyl ester, m.p. 139°. We suspected this to be a nepetalinic acid but it did not correspond to any of the known nepetalinic acids and has not yet been further investigated. The di-basic acid regenerated from the insoluble barium salt had m.p. 87·5–88·5°, $[\alpha]_D^{27}$ −40°, which indicated that it was the enantiomorph of the nepetalinic acid m.p. 85°, $[\alpha]_D$ +30·2° [6] derived from nepetalactone and also known to arise from the oxidation of *iso*iridomyrmecin.[3,4] An equimolar mixture of the two optical isomers (a sample of the (+)-acid was kindly provided by Professor S. M. McElvain) melted, after crystallisation from ether–light petroleum, at 126·5–127·5° and had no measurable rotation, thus confirming the stereochemical relationship of the two acids. It should be noted that the configurational relationship of nepetalactone to L-citronellal follows by way of L-pulegone and its degradation to (+)-α-methylglutaric acid.[7] Hence it is clear that the iridodial and *iso*iridomyrmecin obtained from D-citronellal are in the same D- series and are enantiomorphs of the natural products.

Treatment of the dialdehyde (X) with warm aqueous alkali and lactonisation of the resulting δ-hydroxy acid by means of mineral acid gave a crystalline compound, m.p. 58·5–59°, $[\alpha]_D^{26}$ +56°, which formed a hydrazide, m.p. 118–119° and therefore must be D-*iso*iridomyrmecin (XI). Naturally occurring *iso*iridomyrmecin is reported to have m.p. 58–59°, $[\alpha]_D$ −62°, and its hydrazide to melt at 118°.[3]

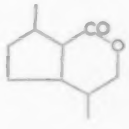
The production of nepetalinic acids by oxidation of our synthetic lactonic mixture demonstrated that it contained substances possessing either or both of the bicyclic



XI



XII



XIII

[10] H. Meerwein, *J. pr.* **97**, 225 (1918); *Ber.* **53**, 1829 (1920).

δ-lactone structures (XII) and (XIII). Standard techniques failed to separate the mixture; eventually a quantity (20 per cent of the total weight) of crystalline lactone was isolated by a procedure known to separate *iso*iridomyrmecin from its stereoisomers.[4] The beautifully crystalline substance was in every respect identical with the specimen of D-*iso*iridomyrmecin previously prepared from D-iridodial.

We examined several alleged sources of L-citronellol but were unable to acquire a supply of this substance or of L-citronellal which was adequately optically homogeneous. We are all the more greatly indebted to Mr. E. E. Boake for the provision of a quantity of L-citronellal, kindly prepared for us in the Research Laboratories of Messrs. A. Boake, Roberts & Co. Ltd. With this material the synthesis was repeated in the correct stereochemical series and gave as the end product L-*iso*iridomyrmecin, which was identical with the lactone isolated from *Iridomyrmex nitidus*.

It must be emphasised that the L-citronellal put at our disposal was a partially synthetic material; the infra-red spectrum showed that it was a mixture of approximately 40 per cent α- and 60 per cent β-citronellal, while the D-citronellal used by us existed exclusively in the β-form.

The α-form of L-citronellal, however, was apparently eliminated when reaction of the aldehyde with ethylene glycol produced the cyclic acetal (V) in unexpectedly low yield (34 per cent),* together with a large amount of polymer; the acetal showed no absorption at 11·25 μ (terminal methylene group) in its infra-red spectrum.

Thereafter the synthesis proceeded essentially along the lines worked out in detail in the D-series. Owing to the limited amount of laevo-rotatory material available, fractional distillation did not completely free the alicyclic dialdehyde (X) from the higher boiling aliphatic isomer (IX), but the latter was obtained in pure form and characterised as the bis-2:4-ninitrophenylhydrazone. Both dialdehydes were converted by the previously described methods into the same crystalline lactone, which was obtained in the form of very long, colourless prisms, m.p. 57·5–58°, undepressed on admixture with authentic *iso*iridomyrmecin (kindly supplied by Dr. G. W. K. Cavill), $[\alpha]_D^{25}$ −56°. A mixture prepared by dissolving equimolar amounts of D- and L-*iso*-iridomyrmecin crystallised very slowly after most of the solvent had been removed, and melted at 32–34°, $[\alpha]_D \pm 0°$.

In order to obtain a sample of pure L-iridodial (X) a small quantity of a mixture of both isomeric dialdehydes (IX) and (X) was treated with a solution of dilute hydrochloric acid in acetone under the conditions known to effect the ring closure (IX → X) Distillation provided as the lowest boiling fraction a liquid whose infra-red absorption spectrum was consistent with the structure (X). This substance formed a bis-2:4-dinitrophenylhydrazone, m.p. 228° (decomp.) which was identical with the corresponding derivative of natural iridodial (undepressed mixed melting point).

Cavill *et al.*[4] found the infra-red absorption due to the carbonyl group of iridomyrmecin at 5·74 μ and that of *iso*iridomyrmecin at 5·69 μ (both spectra in carbon tetrachloride). The infra-red absorption spectra of Nujol mulls of our synthetic L-*iso*iridomyrmecin (Fig. 1) and its enantiomorph were identical, each showing a carbonyl band at 5·76 μ. An authentic specimen of iridomyrmecin (for which we are greatly indebted to Professor M. Pavan) (Fig. 2) showed the carbonyl frequency also at 5·76 μ.

* Recently Messrs. A. Boake, Roberts and Co. Ltd. sent us a sample of L-citronellal containing less than 20% of the α-form; this material gave a much improved yield of cyclic acetal (45%).

Bio-assays* demonstrated that there is no difference in the insecticidal activity of natural iridomyrmecin and the two epimeric synthetic iridolactones, within the limits of the experimental method.

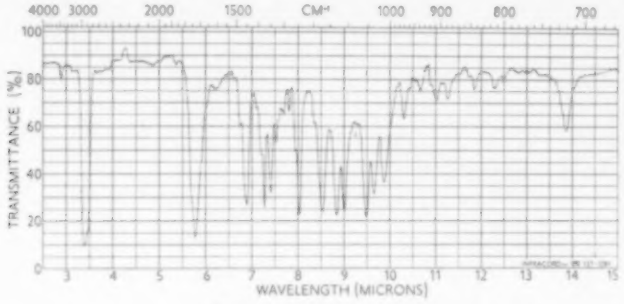


FIG. 1. L-*iso*Iridomyrmecin.

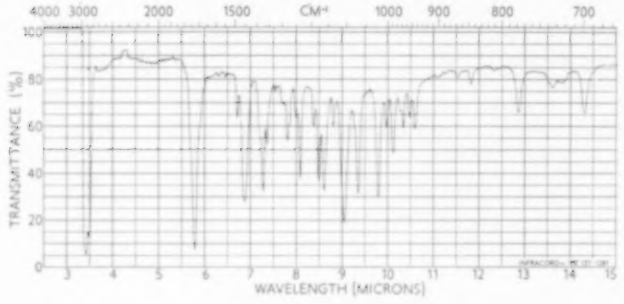


FIG. 2. Iridomyrmecin.

EXPERIMENTAL

Unless otherwise indicated, light petroleum means the fraction of b.p. 40–60°. Extracts were normally dried over anhydrous magnesium sulphate. Infra-red spectra of solids were determined for Nujol mulls.

D(+)-2:6-*Dimethyl*-8:8-*ethylenedioxyoct*-2-*ene* (V)

A mixture of D-citronellal $[\alpha]_D^{22}$ +11·6° (214 g), ethylene glycol (100 cc), benzene (600 cc) and toluene-*p*-sulphonic acid (approx. 100 mg) was refluxed for 12 hr under a Dean–Stark water separator. The solution was diluted with ether, washed with aqueous sodium hydrogen carbonate and water, dried and evaporated. Fractionation of the residue yielded the *cyclic acetal* of D-citronellal as a colourless liquid (190 g), b.p. 125–130°/18 mm, $[\alpha]_D^{22}$ +3·02° (homog.) (Found: C, 73·1; H, 11·1. $C_{12}H_{22}O_2$ requires: C, 72·8; H, 11·1%).

D(+)-2:6-*Dimethyl*-8:8-*ethylenedioxyoct*-2-*en*-1-*al* (VI)

Freshly sublimed selenium dioxide (34 g), dissolved in ethanol (200 cc), was added over a period of 2 hr to a vigorously stirred solution of the above acetal (60 g) in ethanol (100 cc), warmed at 50°. The bath temperature was slowly raised to 95–100° and the mixture stirred and refluxed for 24 hr. When cold it was filtered, the solvent removed *in vacuo* and the residue dissolved in ether, washed with aqueous sodium hydrogen carbonate, dried and fractionally distilled. The fraction b.p. 114–116°/0·2 mm (32·6 g) was stirred for 6 hr with a solution of sodium sulphite heptahydrate (157 g) and sodium

* We are grateful to Shell Research Limited for tests carried out at Woodstock Agricultural Research Centre.

VOL. 6 1959

hydrogen carbonate (90 g) in water (900 cc), and undissolved oil extracted with ether. The ice cold aqueous solution was basified with 10 per cent aqueous sodium hydroxide solution (ca. 450 cc) and repeatedly extracted with ether. After the washed and dried extract was freed from the solvent the *aldehyde* (VI) (23·85 g) was obtained as a colourless oil which was sufficiently pure for use in the next stage. A sample distilled at b.p. 100–106°/0·1 mm and had $[\alpha]_D^{17}$ +5·95° (homog.) (Found: C, 67·5; H, 9·7. $C_{12}H_{20}O_3$ requires: C, 67·9; H, 9·4%). The infra-red spectrum had bands at 3·70 (aldehydic C—H), 5·92 (conjugated C=O) and 6·10 μ (conjugated C=C).

D-2:6-*Dimethyl*-8:8-*ethylenedioxyoct*-2-*enoic acid* (VIII)

A solution of sodium hydroxide (1·24 g) in water (50 cc) was added dropwise at room temperature to a well-stirred mixture consisting of the above aldehyde (1·5 g) in ethanol (23 cc) and silver nitrate (1·24 g) in water (13 cc). After stirring for 3 hr the reaction mixture was filtered and the filtrate concentrated *in vacuo*, and any neutral material extracted with ether. Acidification of the aqueous alkaline solution with dilute sulphuric acid precipitated the *acid* (VIII; 1·59 g) as a pale yellow, thick oil which was evaporatively distilled at 200–205°/0·1 mm (bath temperature) (Found: C, 62·8; H, 8·9. $C_{12}H_{20}O_4$ requires: C, 63·1; H, 8·8%).

Hydrolysis of D-2:6-*dimethyl*-8:8-*ethylenedioxyoct*-2-*en*-1-*al*

The cyclic acetal (VI; 27 g) was refluxed with 50 per cent aqueous acetic acid (270 cc) under nitrogen for 2 hr (oil bath), cooled rapidly and poured into brine. The mixture was extracted with ether and the extract repeatedly washed with water, dilute sodium hydrogen carbonate solution and more water, dried and evaporated. The residue was fractionally distilled to yield as the first main fraction *D*-α-(2-*formyl*-3-*methylcyclopentyl*)-*propional* (X) as a pale yellow liquid (7·55 g), b.p. 78–82°/0·4 mm (Found: C, 70·9; H, 9·3. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·5%). The infra-red spectrum had bands at 3·70 (aldehydic C—H) and 5·82 μ (C=O). As the second main fraction D-2:6-*dimethyloct*-2-*en*-1:8-*dial* (IX) distilled as a colourless liquid, (7·2 g), b.p. 90–93°/0·5 mm. (Found: C, 71·3; H, 9·8. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·5%). The infra-red spectrum had absorption bands at 3·70 (aldehydic C—H), 5·80 (C=O), 5·92 (conjugated C=O) and 6·10 μ (conjugated C=C). D-2:6-*Dimethyloct*-2-*en*-1:8-*dial bis*-2:4-*dinitrophenylhydrazone* was prepared with Brady's reagent and separated from chloroform-ethanol as a brick-red, crystalline powder, m.p. 211–212° (decomp.) (Found: C, 50·1; H, 4·4; N, 21·4. $C_{22}H_{24}O_8N_8$ requires: C, 50·0; H, 4·5; N, 21·2%). The *bis-semicarbazone* of the aliphatic dial (IX) crystallised from ethanol as colourless prisms, m.p. 219° (decomp.) (Found: C, 50·9; H, 7·9; N, 30·1. $C_{12}H_{22}O_2N_6$ requires: C, 51·1; H, 7·8; N, 29·8%).

The *bis*-2:4-*dinitrophenylhydrazone* of the alicyclic dialdehyde (X) crystallised from ethyl acetate–ethanol as orange prisms, m.p. 227° (Found: C, 49·9; H, 4·7; N, 21·2. $C_{22}H_{24}O_8N_8$ requires: C, 50·0; H, 4·5; N, 21·2%). The *bis-semicarbazone* of the dialdehyde (X) formed colourless needles in methanol, m.p. 197–198° (decomp.) (Found: C, 51·0; H, 7·7; N, 30·1. $C_{12}H_{22}O_2N_6$ requires: C, 51·1; H, 7·8; N, 29·8%).

Cyclisation of D-2:6-*dimethyloct*-2-*en*-1:8-*dial* (IX)

The aliphatic dialdehyde (IX) (7·0 g) was refluxed for 1 hour with acetone (100 cc) and 10 per cent hydrochloric acid (2 cc) under nitrogen. The mixture was concentrated on the water bath, diluted with ether and poured into brine. After washing the ethereal layer with aqueous sodium hydrogen carbonate and water, it was dried and evaporated. Fractionation furnished D-α-(2-formyl-3-methyl-*cyclo*pentyl)-propional (X) as a pale yellow liquid (3·5 g), b.p. 74–76°/0·1 mm which was identical with the previously prepared specimen.

D(+)-iso*Iridomyrmecin* (XI)

(a) *From the alicyclic dialdehyde* (X). D-α-(2-Formyl-3-methyl*cyclo*pentyl)-propional (7·1 g) was warmed for 1 hr with N-sodium hydroxide solution (100 cc) under nitrogen. Undissolved material was extracted with ether, the aqueous layer cooled in ice and cautiously acidified with 5 N-hydrochloric acid (20 cc). The colourless precipitate was collected, briefly washed with ice-cold ether, suspended in ether and shaken with 5 N-hydrochloric acid. The organic layer was washed with aqueous sodium hydrogen carbonate and water, dried and evaporated. The residue partly solidified at room temp; repeated crystallisations from light petroleum yielded D-iso*iridomyrmecin* as elongated prisms (1·03 g).

m.p. 58·5–59°, $[\alpha]_D^{26}$ + 56° (*c*, 1·41 in CCl_4) (Found: C, 71·8; H, 9·8. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·5%). The infra-red absorption spectrum showed the carbonyl frequency at 5·76 μ.

(b) *From the aliphatic dialdehyde* (IX) *by Michael condensation.* Anhydrous methanol (50 cc) was added at room temp to D-2:6-dimethyloct-2-en-1:8-dial (11 g) under nitrogen, followed by 10 per cent methanolic sodium methoxide (5 cc). After 16 hr at room temp the brownish solution was refluxed for 8 hr and finally left to cool over night. The solution was then chilled in an ice bath, acidified with dilute hydrochloric acid, poured into brine and thoroughly extracted with ether. The acidic organic extract was kept for 3–5 hr (to complete lactonisation), freed from acidic matter by means of aqueous sodium hydrogen carbonate, washed and dried. Evaporation of the solvent left a brown, mobile liquid (10·3 g) which had a pungent, sweet odour and gave on distillation as the main fraction a colourless liquid (4·85 g), b.p. 87–90°/0·2 mm, $[\alpha]_D^{22}$ −39° (*c*, 1·048 in CCl_4) (Found: C, 71·4; H, 9·5. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·5%). The infra-red spectrum showed a band in the carbonyl region at 5·76 μ. This material could not be induced to crystallise and was evidently a mixture of bicyclic δ-lactones.

A portion of this mixture (1·9 g) was dissolved in warm 2 N-potassium hydroxide solution (26 cc), chilled in ice and 50 per cent aqueous acetic acid (21 cc) was added dropwise with swirling (cf. ref. 4). The colourless precipitate was lactonised as described in section (a) and the resulting solid recrystallised twice from light petroleum to yield the lactone (XI), m.p. 58–59°, which was identical with the previously prepared specimen. The *hydrazide* crystallised from benzene and had m.p. 118–119° (Found: C, 59·8; H, 10·2; N, 13·8. $C_{10}H_{20}O_2N_2$ requires: C, 60·0; H, 10·0; N, 14·0%).

Oxidation of the mixture of lactones obtained from the Michael reaction

Potassium permanganate (5·2 g) was added in small portions during 2½ hr to a stirred solution of the oil, b.p. 87–90°/0·2 mm (3·4 g) in 5 per cent sodium hydroxide solution (40 cc), the temp being kept below 10°. After standing at room temp overnight, the reaction mixture was filtered, undissolved material extracted with ether and the aqueous layer treated with a concentrated solution of barium hydroxide in water. The acid liberated from the crystalline salt was recrystallised twice from light petroleum and was a D(−)-*nepetalinic acid* m.p. 87·5–88·5°, $[\alpha]_D^{27}$ −40° (*c*, 1·44 in $CHCl_3$) (Found: C, 60·3; H, 8·0. $C_{10}H_{16}O_4$ requires: C, 60·0; H, 8·0%). A specimen of its enantiomorph, kindly provided by Professor S. M. McElvain, had m.p. 84–85°, $[\alpha]_D^{28}$ +30·2° (*c*, 2·45 in $CHCl_3$). An equimolar mixture of the two enantiomorphous acids was crystallised from ether-light petroleum to give a *racemic nepetalinic acid*, m.p. 126·5–127·5°, $[\alpha]_D$ ±0°. (Found: C, 60·2; H, 8·1. $C_{10}H_{16}O_4$ requires: C, 60·0; H, 8·0%).

The filtrate and washings from the above crystalline barium salt were treated with hydrochloric acid and the acidic material collected in ether. The crystalline residue (0·50 g) was recrystallised three times from ether-light petroleum, to give a *dicarboxylic acid*, m.p. 142–143°, $[\alpha]_D^{26}$ −16° (*c*, 1·00 in $CHCl_3$) which analysed correctly for a nepetalinic acid. (Found: C, 60·2; H, 8·0. $C_{10}H_{16}O_4$ requires: C, 60·0; H, 8·0%). Its *bis*-p-*bromophenacyl ester* crystallised from ethanol as needles, m.p. 138·5–139·5° (Found: C, 52·5; H, 4·3; Br, 27·1. $C_{24}H_{24}O_6Br_2$ requires: C, 52·6; H, 4·4; Br, 26·9%).

L(−)-2:6-*Dimethyl*-8:8-*ethylenedioxyoct*-2-*ene* (V)

A mixture of L-citronellal, $[\alpha]_D^{28}$ −10·5° (47·8 g), ethylene glycol (22 cc), benzene (200 cc) and toluene-*p*-sulphonic acid (approximately 30 mg) was reacted as described for the preparation of the corresponding enantiomorph. Fractionation yielded the *cyclic acetal* as a colourless liquid (20·7 g), b.p. 120–125°/18 mm, $[\alpha]_D^{26}$ −3·9° (Found: 72·9; H, 11·0. $C_{12}H_{22}O_2$ requires: C, 72·8; H, 11·1%).

L(−)-2:6-*Dimethyl*-8:8-*ethylenedioxyoct*-2-*en*-1-*al* (VI)

The above acetal (20 g), dissolved in ethanol (35 cc), was oxidised with a solution of selenium dioxide (11·4 g) in ethanol (70 cc), and the fraction, b.p. 108–114°/0·25 mm (12·5 g) stirred for 6 hr with a solution of sodium heptahydrate (47 g) and sodium hydrogen carbonate (27 g) in water (270 cc), followed by treatment with dilute sodium hydroxide solution (125 cc); the conditions were those employed for the preparation of the corresponding optical isomer. The *aldehyde* was thus obtained as a colourless oil (10 g), b.p. 88–90°/0·1 mm, $[\alpha]_D^{27}$ −5·45° (Found: C, 67·6; H, 9·7. $C_{12}H_{20}O_3$ requires: C, 67·9; H, 9·4%).

VOL. 6 1959

Hydrolysis of L(−)-2:6-*dimethyl*-8:8-*ethylenedioxyoct*-2-*en*-1-*al*

A solution of the above compound (10 g) in aqueous acetic acid (100 cc of 50%) was refluxed (oil bath) under nitrogen for 2 hr and worked up as previously described in the D-series. Fractionation of the reaction mixture gave: (a) a pale yellow liquid, b.p. 70–72°/0·15 mm (2·35 g), whose infra-red spectrum showed that it consisted chiefly of L-α-(2-formyl-3-methyl*cyclo*pentyl)-propional (X), having absorption bands of appropriate intensity at 3·70 and 5·82 μ, but weak bands at 5·92 and 6·10 μ indicated that some of the aliphatic dialdehyde (IX) contaminated this fraction; (b) a colourless liquid (2·1 g), b.p. 78–82°/0·15 mm, whose infra-red spectrum was in agreement with the structure of pure L-2:6-*dimethyloct*-2-*en*-1:8-*dial* (IX) with bands at 3·70, 5·80, 5·92 and 6·10 μ (Found: C, 70·8; H, 9·6. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·5%); the *bis*-2:4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as brick-red needles, m.p. 211–212° (decomp.) (Found: C, 49·9; H, 4·6; N, 20·2. $C_{22}H_{24}O_8N_8$ requires: C, 50·0; H, 4·5; N, 21·2%).

L-α-(2-*Formyl*-3-*methylcyclopentyl*)-*propional bis*-2:4-*dinitrophenylhydrazone*

L-2:6-Dimethyloct-2-en-1:8-dial (0·4 g), which was contaminated with some of the cyclic dialdehyde (X), was refluxed for 1 hr with acetone (35 cc) and 10 per cent hydrochloric acid (1 cc) under nitrogen. Most of the solvent was then evaporated in an inert atmosphere, the residue dissolved in ether, washed and dried. Evaporative distillation gave an almost colourless oil (0·19 g) which distilled at 85–90°/0·1 mm (bath temperature); the infra-red spectrum showed that this was L-α-(2-formyl-3-methyl*cyclo*pentyl)-propional (X) (bands at 3·10 and 5·82 μ). The entire material was converted into the *bis*-2:4-*dinitrophenylhydrazone*, which formed orange prisms in ethyl acetate–ethanol, m.p. 228° (decomp.), undepressed on admixture with authentic iridodial bis-2:4-dinitrophenylhydrazone (Found: C, 50·3; H, 4·3; N, 21·1. $C_{22}H_{24}O_8N_8$ requires: C, 50·0; H, 4·5; N, 21·2%).

L(−)-Iso*iridomyrmecin* (XI)

(a) *From the fraction containing the alicyclic dialdehyde* (X). The above fraction, b.p. 70–72°/0·15 mm (2·22 g) was warmed with 2 N-potassium hydroxide solution (30 cc) for 1 hr under nitrogen Undissolved material was extracted with ether, the aqueous solution cooled in ice and acidified with 8 N-acetic acid (25 cc). The colourless precipitate was treated in the manner described for the corresponding experiment in the D-series. The lactone thus obtained (273 mg) crystallised from light petroleum as elongated colourless prisms, m.p. 57·5–58°, $[\alpha]_D^{25}$ −56° (*c*, 1·09 in CCl_4); the melting point was undepressed on admixture with genuine *iso*iridomyrmecin (kindly supplied by Dr. G. W. K. Cavill), which showed that our material was L-iso*iridomyrmecin* (Found: C, 71·7; H, 9·2. $C_{10}H_{14}O_2$ requires: C, 71·4; H, 9·5%). The infra-red spectrum was identical with that of its enantiomorph.

(b) *From* L-2:6-*dimethyloct*-2-*en*-1:8-*dial* (IX) *by Michael condensation.* A solution of the aliphatic dialdehyde (IX; 1·69 g) in anhydrous methanol (8 cc) was treated with 10 per cent methanolic sodium methoxide (1 cc) and worked up under the conditions described for the corresponding experiment in the D-series. The resulting lactone was identical with L(−)-*iso*-iridomyrmecin.

An equimolar mixture of D- and L-*iso*iridomyrmecin failed to crystallise from light petroleum, but after slow evaporation of the solvent long thread-like crystals were obtained, m.p. 32–34°, which had no measurable rotation.

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SYNTHESES WITH PYRIMIDINE-LITHIUM COMPOUNDS*†

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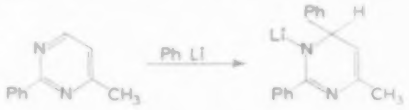
Abstract—The principles of the preparation, reactivity and use of organolithium compounds is briefly discussed in relation to recent work with N-heterocyclic derivatives. The synthesis of thymine-$C^{14}H_3$ and 5-ethyluracil from a pyrimidine-lithium intermediate, and the separation of uracil and thymine by ion-exchange chromatography, are described. It is shown that such syntheses can be carried out with compounds containing active hydrogens by taking advantage of the higher reactivity of lithium-carbon bonds, and this is illustrated in a synthesis of thymidine from 5-bromodeoxyuridine.

VOL. 6 1959

THERE are several difficulties encountered in attempting to use in synthesis lithium derivatives of heterocyclic compounds containing the —C=N— group, since the use of organolithium compounds depends on their reactivity towards multiple bonds between carbon and hetero atoms. Thus in pyridines, at room temperature, organolithium compounds add very readily to the azomethine linkage,[1] but fully aromatic lithium pyridyls can be prepared from the bromocompounds and butyllithium by halogen-lithium exchange at low temperatures (−35°)[2] at which the rate of the azomethine addition reaction is greatly reduced. In certain compounds such as 4:5-dimethylthiazole,[3] 1-phenyl-3-methylpyrazole[4] and 1-substituted imidazoles,[5] lithium derivatives can be prepared at room temperature, and the azomethine linkage appears to be less reactive.

In pyrimidines, the azomethine linkages are *meta* to each other and the carbon atoms adjacent to nitrogen are therefore particularly susceptible to nucleophilic attack. This is seen when one compares the reaction of organolithium compounds with α- and β-picoline type derivatives and with methylpyrimidines respectively. Picolines metallate in the methyl group; for example, with phenyllithium, α-picoline gives 2-pyridylmethyllithium. On the other hand, pyrimidines with a methyl group in an analogous (2, 4 or 6) position usually react by addition, as in the following example:[6]



Pyrimidines would be expected to polymerise in attempted preparations of lithium derivatives, although the use of sufficiently low temperatures may minimise this, as

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‡ Present address: University Chemical Laboratory, Lensfield Road, Cambridge.

[1] K. Ziegler and H. Zeiser, *Ber.* **63,** 1847 (1930).
[2] H. Gilman and S. M. Spatz, *J. Amer. Chem. Soc.* **62,** 446 (1940).
[3] M. Erne and H. Erlenmeyer, *Helv. Chim. Acta* **31,** 652 (1948).
[4] H. R. Snyder, F. Verbanac and D. B. Bright, *J. Amer. Chem. Soc.* **74,** 3243 (1952).
[5] D. A. Shirley and P. W. Alley, *J. Amer. Chem. Soc.* **79,** 4922 (1957).
[6] T. D. Heyes and J. C. Roberts, *J. Chem. Soc.* 328 (1951).

was shown by Langley,[7] for example, in a synthesis of orotic acid-$C^{14}O_2H$ from 4-bromo-2:6-diethoxypyrimidine by halogen-lithium exchange and reaction with carbon dioxide.

A very interesting point, not previously discussed, is that pyrimidine-lithium compounds have a pronounced orange colour. This can perhaps be explained by analogy with the spectrum of pyridine, which shows in addition to the bands present in benzene, a band due to an $n \rightarrow \pi$ transition (the lone pair of electrons on nitrogen shifting to an anti-bonding orbital). In acid solution, of course, this band disappears. In the dimethoxy-pyrimidine-lithium compound, the electrons of the C—Li bond will be almost entirely localised on the C atom and easily excited, so that the colour may be ascribed to a $\sigma \rightarrow \pi$ transition. If so, replacement of the methoxyl groups in the ring by more electronegative groups should shift the absorption to longer wavelengths.*

New evidence on the mechanism of the halogen-metal exchange reaction, by which heterocyclic compounds are usually prepared, has been recently presented and discussed,[8] and is consistent with the idea that the exchange takes place via an addition complex and without any change in the configuration of the carbon atom at which reaction takes place.

The work to be described depends on two reactions, halogen-metal exchange (1), and the coupling reaction in which the organic radicals join and the lithium halide is formed (2):

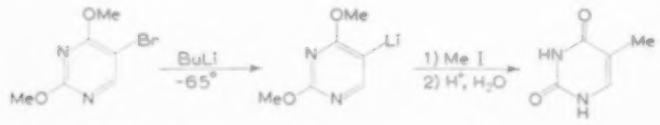
$$RLi + R'X \qquad (1)$$

$$RX + R'Li \rightleftharpoons R{-}R' + LiX \qquad (2)$$

Reaction (1), where X = H, depends on the relative acidities of RH and R′H; the initial reaction appears to be the nucleophilic attack on hydrogen (of RH) by the anion (R'^-) of the reagent.[9,10] When X = halogen, the reaction is an equilibration between the lithium salts of the two weak acids, RH and R′H, and therefore largely depends on the relative stabilities of R^- and R'^-. Pyrimidine-lithium compounds are therefore readily formed by reaction (1).

Reaction (2) depends mainly on the nature of the halogen. The reaction is negligible when X = Cl, and in general iodides have to be used, as in the present work.

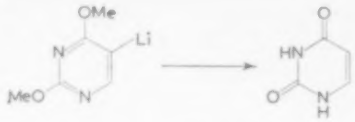
Thymine has now been synthesised employing these basic reactions by the conversion of 5-bromo-2:4-dimethoxypyrimidine to the lithium derivative, reaction with methyl iodide, and hydrolysis:



* The author thanks Prof. H. C. Longuet-Higgins for a discussion of this point.

[7] B. W. Langley, *J. Amer. Chem. Soc.* **78**, 2136 (1956).
[8] G. Wittig and U. Schollkopf, *Tetrahedron* **3**, 93 (1958).
[9] D. Bryce-Smith, *J. Chem. Soc.* 1079 (1954).
[10] D. Bryce-Smith, V. Gold and D. P. N. Satchell, *J. Chem. Soc.* 2473 (1954).

However, paper chromatography showed that the product was contaminated by uracil, formed by reaction of water with pyrimidine-lithium compound which had not reacted with methyl iodide:



By carbonation before treating the reaction mixture with water, the formation of uracil was much reduced; any uracil-5 carboxylic acid formed is easily separated from thymine. Thymine-$C^{14}H_3$, for which this synthesis was designed, was prepared in 40 per cent yield from $C^{14}H_3I$. Previously, methyl-labelled thymine was only available from a five-step synthesis, with a yield of purified material of 6·4 per cent.[11] From the same pyrimidine-lithium intermediate and ethyl iodide, 5-ethyluracil, otherwise not readily available, has been synthesised, and seems to merit biological testing as an analogue of thymine.

In order that very pure thymine could be prepared by this method, the separation of appreciable quantities of thymine and uracil was investigated. The method of Cohn[12] was found to give almost no separation, but when Dowex-1-chloride was used and elution begun with an ammonium hydroxide–ammonium chloride solution of high pH, uracil was eluted. After changing to ammonium chloride as eluant, pure thymine was obtained.

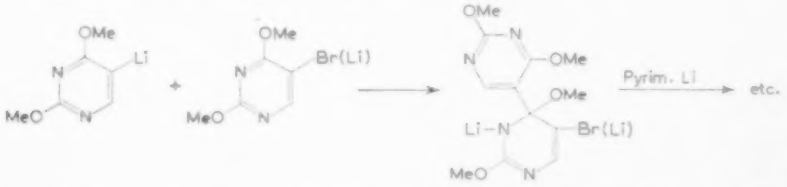
An unexpected finding was that the yield in the above type of reaction depended on the method of preparation of the butyl-lithium used (although in all cases this was estimated by double titration). The yield was higher when butyllithium was prepared from butyl chloride* than when it was prepared from butyl bromide. One possible explanation is that there is unreacted butyl bromide present, furthering a reaction of type (2):

$$\text{Pyrim. Li} + \text{BuBr} \rightarrow \text{Pyrim. Bu} + \text{LiBr}$$

which in any case must occur to some extent, since butyl bromide is a product of reaction (1):

$$\text{Pyrim. Br} + \text{BuLi} \rightarrow \text{Pyrim. Li} + \text{BuBr}$$

However, the principal side-reaction—perhaps, in fact, the major reaction—is the formation of polymeric compounds by the addition of the pyrimidine-lithium compound across an azomethine linkage in another molecule:



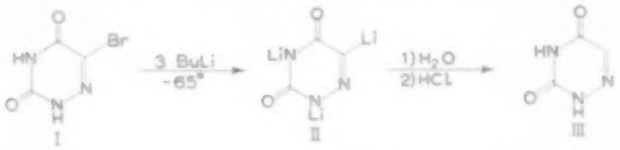
These reactions are very sensitive to traces of impurity. In the case of the lithium

* Sometimes this reaction fails completely, an observation also made by other investigators, though not recorded in the literature. Invariably the lithium metal was responsible.

[11] R. B. Henderson, R. M. Fink, and K. Fink, *J. Amer. Chem. Soc.* **77**, 6381 (1955).
[12] W. E. Cohn, *Science* **109**, 377 (1949).

alkenyls,[13,14] the important factor was the purity of the halide from which they were prepared. In the present instance, the purity of the halide (e.g. methyl iodide) used in the subsequent coupling reactions seems to be more important. Whereas Grignard reactions are catalysed by traces of iodine, the use of impure methyl iodide containing iodine greatly reduces the yield with pyrimidine-lithium compounds. (Radioactive methyl iodide decomposes very quickly, and should be supplied and used dissolved in an inert anhydrous solvent.) It was observed that iodine catalyses the formation of polymeric products from butyllithium in ether, and it seems to have a similar effect on pyrimidine-lithium compounds.

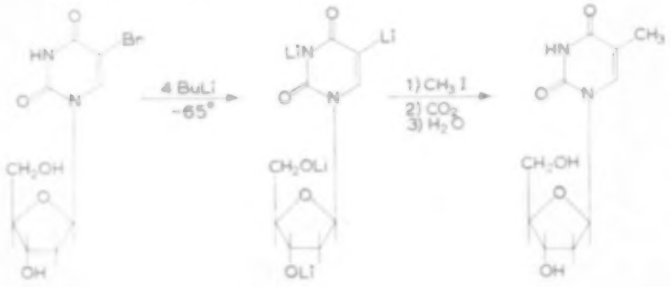
In the reactions so far described, alkoxypyrimidines have been used, with later hydrolysis to yield the products with active hydrogen atoms. But these reactions can be carried out without protecting the active hydrogens in the ring, as was first shown by Chang and Ulbricht[15] in the case of 5-bromo-6-azauracil (I):



I II III

6-Azauracil (III) was obtained in 17 per cent yield in this reaction, probably the first employing an intermediate containing more than two lithium atoms. (Some reactions have previously been carried out with compounds containing *one* active hydrogen atom, e.g. bromo-naphthols.[16]) Similarly, 5-bromouracil can be converted to uracil, or to thymine, as indicated by paper chromatography and ultra-violet spectra.

The synthesis of thymidine from 5-bromodeoxyuridine has been studied with a view to developing a method for the preparation of C^{14}-labelled thymidine, otherwise only available by enzymatic synthesis.[17]



IV

The main difficulty in this synthesis is that it is a heterogeneous reaction. The tetra-lithium intermediate (IV) is insoluble in tetrahydrofuran (as is trilithium uracil) and also in other solvents which can be used for this reaction (ether, dioxan–ether, dioxan–tetrahydrofuran, dimethoxyethane), whereas the other lithium derivatives described, including the trilithiumazauracil (II), are soluble. Chromatography of the

[13] E. A. Braude and C. J. Timmons, *J. Chem. Soc.* 2000 (1950).
[14] E. A. Braude and J. C. Coles, *J. Chem. Soc.* 2014 (1950).
[15] P. K. Chang and T. L. V. Ulbricht, *J. Amer. Chem. Soc.* **80**, 976 (1958).
[16] S. V. Sunthankar and H. Gilman, *J. Org. Chem.* **16**, 8 (1951).
[17] M. Friedkin and D. Roberts, *J. Biol. Chem.* **207**, 257 (1954).

products showed the presence of considerable quantities of deoxyuridine and of unreacted 5-bromodeoxyuridine in addition to thymidine, and very little material having the properties of a compound containing N^1-methyl or O-methyl groups. The yield of thymidine was therefore essentially limited by (1) incomplete halogen-lithium exchange, and (2) incomplete reaction with methyl iodide, but nevertheless it appeared that at the temperature of the reaction a real distinction between the reactivity of lithium-carbon bonds as against that of lithium-nitrogen and lithium-oxygen bonds had been achieved. This is presumably due to the high nucleophilicity of a carbon atom having an appreciable negative charge.

Tetrahydrofuran proved to be the best solvent for this reaction. Formation of deoxyuridine was reduced by carbonation after allowing time for the methyl iodide to react, but could not be avoided completely. Various methods were tried for the separation of deoxyuridine and thymidine on ion-exchange columns, including gradient elution with formate and phosphate buffers on Dowex-1-formate, but satisfactory separation was not achieved. The purification was carried out in three stages: (1) removal of salts by washing on Dowex-1-formate; (2) separation from deoxyuridine, 5-bromodeoxyuridine, 5-carboxydeoxyuridine and other impurities by paper chromatography using the ethyl acetate–phosphate buffer system;[18] and (3) final chromatography to remove impurities from the paper and salts, on Dowex-1-formate.

The yield of thymidine, whose purity was also checked by biological assay, was 10 per cent. For a reaction of this type, this seemed satisfactory. A lower yield was obtained in one synthesis using C^{14}-methyl iodide. The conditions of this reaction were somewhat different. The radioactive methyl iodide was not supplied in solution and had partially decomposed, and the reaction had to be run on a larger scale without opportunity of a cold run. In a heterogeneous reaction, this may well affect the yield. On the scale originally used, with pure methyl iodide, the yield is reproducible, and this represents a convenient chemical method for the synthesis of thymidine-$C^{14}H_3$.

It is possible that the methods described in this paper could be used to synthesise pyrimidine (or other heterocyclic) C-glycosides from suitable lithium intermediates and glycosyl halides. The feasibility of such a method would depend on the relative reactivities of the halogen and the ester groups in the glycosyl halide at the low temperature of the reaction.

EXPERIMENTAL*

Solvents and reagents. Ether and tetrahydrofuran were distilled from lithium aluminium hydride, using a Vigreaux column. *n*-Butyl bromide and *n*-butyl chloride were dried for 30 min over phosphorus pentoxide, decanted and distilled. Methyl and ethyl iodide were freshly distilled.

n-*Butyllithium* was prepared from *n*-butyl bromide[19] or from *n*-butyl chloride.[20] In the latter case, freshly-prepared lithium wire had to be used to obtain consistent results. The butyllithium was estimated by double titration.[21]

Thymine, using butyllithium prepared from butyl bromide. An ethereal solution of butyllithium (0·53 N, 5 ml) was added in one min to a stirred solution of 5-bromo-2:4-dimethoxypyrimidine[22]

* Melting points are uncorrected. Analysis by Huffman Microanalytical Laboratories, Wheatridge, Colorado.

[18] W. H. Prusoff, *J. Biol. Chem.* **215**, 809 (1955).
[19] H. Gilman, J. A. Beel, C. G. Branner, M. W. Bullock, G. E. Dunn and L. S. Miller, *J. Amer. Chem. Soc.* **71**, 1499 (1949).
[20] H. Gilman, E. A. Zoellner and W. M. Selby, *J. Amer. Chem. Soc.* **54**, 1957 (1932).
[21] H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.* **66**, 1515 (1944).
[22] G. E. Hilbert and E. F. Jansen, *J. Amer. Chem. Soc.* **56**, 134 (1934).

(580 mg) in tetrahydrofuran (10 ml) at −65° (dry ice-*iso*propanol) in an atmosphere of nitrogen. Methyl iodide (380 mg) in ether (5 ml) was added to the orange-coloured solution, discharging most of the colour. After stirring for 10 min at −65°, excess dry ice was added, the cooling-bath removed, and stirring continued for 1 hr. The solution was poured into water (10 ml) and extracted with ether, sodium chloride and a few crystals of sodium thiosulphate being added to the aqueous layer. After drying over anhydrous magnesium sulphate, the ether was removed by blowing dry air onto the surface of the solution. The residue was refluxed with hydrochloric acid (6 N, 4 ml) for 2 hr, evaporated to dryness, and sublimed *in vacuo*, leaving a considerable residue of polymeric material. Resublimation at 200°/12 mm† gave thymine, m.p. and mixture m.p. 314–316°. Yield, 95 mg (29%). The yield in other runs was always 25–30%.

Thymine-$C^{14}H_3$, using butyllithium prepared from butyl chloride. The procedure was as above, using ethereal butyllithium (0·81 N, 3·4 ml, 2·7 m moles), 5-bromo-2:4-dimethoxypyrimidine (602 mg, 2·5 mM), tetrahydrofuran (10 ml), methyl iodide-C^{14} (New England Nuclear Co. 358 mg, 2·5 mM, 5 mC, 1·97 mC/mM) in ether (5 ml) transferred by pipette. Yield of resublimed product, 158 mg (40%). Specific activity, 1·95 mC/mM. UV spectrum: max/min 264/233 mμ (pH 7) (cf. thymine, 264/233; uracil, 259/227 mμ[22]). Paper chromatography confirmed the identity of thymine, and indicated the presence of a trace of (non-radioactive) uracil.

5-Ethyluracil. The same procedure was used, with ethereal butyllithium (0·62 N, 5 ml, from butyl bromide), 5-bromo-2:4-dimethoxypyrimidine (555 mg), tetrahydrofuran (10 ml), ethyl iodide (792 mg, 2 moles) in ether (5 ml). The yield of sublimed material was 110 mg (32%). A portion was recrystallised from methanol and resublimed, m.p. 301–303° dec.

(Found: C, 51·7; H, 5·8; N, 20·1. Calc. for $C_6H_8N_2O_2$: C, 51·4; H, 5·8; N, 20·0%).

Separation of thymine and uracil. Thymine (30 mg) and uracil (30 mg) were dissolved in aqueous sodium hydroxide (0·1 N, about 30 ml) and put on a column of Dowex-1-chloride (40 × 1 cm). The eluting solution was made up as follows: 1 volume of ammonium chloride (0·2 N) was diluted with 9 vols of ammonium hydroxide (0·23 N) to give a solution 0·02 N in chloride ion. This solution (pH ~ 10·4) was adjusted to pH 12·2 with sodium hydroxide (6 N). The eluate was collected at the rate of about 20 ml every 30 min. After 1 l. had been collected, uracil began to come off the column (this was followed by optical density at 280 mμ). When the uracil had come off, the eluting solution was changed to ammonium chloride (0·025 N), and after about 200 ml the thymine came off in about 60 ml. The recovery of thymine was 85 per cent, as estimated by optical density, and was purer than that used at the beginning of the experiment.

Uracil from 5-bromouracil. 5-Bromouracil (dried at 80° *in vacuo* 95·5 mg, 0·5 mM) was dissolved in hot dioxan (purified, 15 ml), ether (15 ml) and N-ethylmorpholine (purified, 10 ml) added, the solution cooled to −50° in an atmosphere of nitrogen, ethereal butyllithium (0·38 N, 4·3 ml, 1·65 mM, from butyl chloride) added, giving a white precipitate. Water (2 ml) was added, stirred vigorously, and the cooling bath removed. Paper chromatography and UV spectra showed the presence of uracil (~15%) and unchanged 5-bromouracil.

Thymine from 5-bromouracil. The same method was used, with tetrahydrofuran as solvent. After reaction with methyl iodide, water was added without prior carbonation. Paper chromatography revealed the presence of uracil, thymine (~15%), and 5-bromouracil.

Thymidine. 5-Bromodeoxyuridine (Cyclo Chemical Corp. dried at room temp *in vacuo*, 153·5 mg, 0·5 mM) was dissolved in hot tetrahydrofuran (15 ml) and cooled to −60° in an atmosphere of nitrogen. Ethereal butyllithium (0·71 N, 3·1 ml, 2·2 mM, from butyl chloride) was added to the stirred solution, giving a white precipitate. Methyl iodide (71 mg, 0·5 mM) in ether (5 ml) was added, and the mixture stirred for 20 min while the temp rose to −35°. Excess dry ice was added and the mixture stirred until the temp rose to 0°. The yellow solution was poured into water and dry air blown onto the surface to remove tetrahydrofuran. Ammonium hydroxide solution was added (pH 11, 30 ml) and put on a Dowex-1-formate column (10 × 2 cm) which was successively eluted with ammonium hydroxide (pH 11, 400 ml), water (250 ml), 0·001 N formic acid (200 ml) and finally 0·02 N formic acid. Elution was followed by optical density at 260 mμ and the pyrimidine nucleosides began to come off the column 250 ml after changing to 0·02 N formic acid. The solution containing the nucleosides was lyophilised, the residue dissolved in a little water and put on three 30-inch sheets of Whatman No. 3 paper and run in ethyl acetate–phosphate buffer for 6 hr. The thymididne

† Uracil-5-carboxylic acid does not sublime or decarboxylate under these conditions.

[22] D. Shugar and J. J. Fox, *Biochim. Biophys. Acta* **9**, 199 (1952).

areas were cut out, cut into small pieces, and extracted in a mixing blender with ammonium hydroxide (pH 11, 2 × 200 ml). The filtered solution was put on a Dowex-1-formate column and eluted with water and formic acid as before, to give 365 ml of solution with a maximum optical density of 1·37 at 267 mμ. This represents a yield of 10·3%. The product had the right UV spectrum, max/min 267/235 acid, 267/245 mμ base, and in five solvent systems (butanol–water, butanol–ammonia, *iso*propanol–hydrochloric acid, *iso*propanol–ammonia, ethyl acetate–phosphate buffer) gave a single spot, with the same R_F as a sample of authentic thymidine run concurrently. Biological assay (*Streptococcus faecalis*) indicated a purity of at least 90 per cent.

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VOL.
6
1959

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ETUDES CINETIQUES DES REACTIONS DE SOLVOLYSE DE CHLORURES D'α-PHENYLETHYLE SUBSTITUES

EQUATIONS DE HAMMETT, WINSTEIN-GRÜNWALD ET TOMMILA

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Abstract—The kinetic study of the solvolysis of *m*-CH_3, *p*-CH_3, *m*-OCH_3, *p*-Cl, *m*-Cl and *p*-F substituted α-phenylethyl chlorides has been carried out in the following media:

water 20·5%–dioxane 79·5%
water 49·3%–dioxane 50·7%
water 66·66%–dioxane 33·33%
water 5·3%–dioxane 25·8%–formic acid 69·7%
water 6·1%–dioxane 39·8%–formic acid 54·1%
water 5·8%–dioxane 60·2%–formic acid 34·0%

Correlation of solvolysis rates has been made with the equations of Hammett, Winstein–Grünwald and Tommila.

INTRODUCTION

Différentes tentatives de corrélation des vitesses de réaction ont été réalisées au cours des dernières années. Les plus brillantes sont celles de Hammett, Winstein–Grünwald et Tommila, qui ont fait, depuis leur publication, l'objet de nombreuses études critiques.

Le but de ce travail consiste à étudier à l'aide des équations énoncées par ces auteurs, les rôles respectifs du solvant et de la variation de densité électronique au cours des réactions de solvolyse de dérivés réagissant par un mécanisme monomoléculaire limite.

Ingold et plusieurs auteurs ont montré que le chlorure d'α-phényléthyle réagit par un mécanisme S_N1, même lorsque le pouvoir nucléophile du solvant n'est pas négligeable. C'est pourquoi nous avons choisi d'étudier les vitesses de solvolyse de ce dérivé substitué par l'un des groupes suivants: *p*-CH_3, *m*-CH_3, *p*-Cl, *m*-Cl, *p*-F ou *m*-CH_3 dans les solvants suivants:

eau 20·5%–dioxanne 79·5%
eau 49·3%–dioxanne 50·7%
eau 66·66%–dioxanne 33·33%
eau 5·3%–dioxanne 25·8%–acide formique 69·7%
eau 6·1%–dioxanne 39·8%–acide formique 54·1%
eau 5·8%–dioxanne 60·2%–acide formique 34·0%

A. *Relation de Winstein–Grünwald*

Winstein et Grünwald, tentant de relier entre elles les vitesses de solvolyse monomoléculaire d'un produit dans différents milieux, ont proposé en 1948 l'équation bien connue:

$$\log k/k_0 = mY \qquad (1)$$

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où k = constante de vitesse à une température donnée de la solvolyse d'un composé déterminé; k_0 = constante de vitesse de ce dérivé dans un milieu de référence; m = un paramètre; Y = le pouvoir ionisant du solvant.

Tous les paramètres intervenant dans cette équation sont calculés à la même température, habituellement 25°. Winstein et Grünwald ont vérifié en première approximation la relation (1) pour une série de dérivés organiques engagés dans des réactions de substitution monomoléculaire.[1,2] Ils ont montré de plus que lorsque la réaction n'est pas S_N1, la relation (1) n'est pas vérifiée.

Bases théoriques de la relation de Winstein–Grünwald

En vue d'expliquer les écarts observés à la relation de Winstein–Grünwald Wilputte *et al.*[3–6] ont tenté de fournir une base théorique à cette relation empirique.

Soit deux halogénures A et B, subissant la solvolyse suivant un mécanisme S_N1, dans deux milieux a et b, et ΔF^*, l'énergie d'activation de ces réactions; si l'on suppose que:

$$\Delta F^* = \Delta F_0^* + L'f \tag{2}$$

où ΔF_0^* est l'énergie libre indépendante du milieu; f = fonction des propriétés ionisantes et électrophiles du solvant; L' = constante caractéristique de l'halogénure,

on en déduit que $$\frac{\log k_{Aa} - \log k_{Ab}}{\log k_{Ba} - \log k_{Bb}} = L_A/L_B = m_{AB} \tag{3}$$

L'équation (3) est l'expression générale de la relation de Winstein–Grünwald.

L'examen des approximations de base (2) permet de justifier aisément les écarts observés. En effet, le second terme rend compte de l'action du solvant sous forme d'un produit de deux facteurs dont l'un ne dépend que du solvant et dont l'autre ne dépend que du produit. Les résultats obtenus semblent montrer que ces approximations ne se justifient que lorsque les deux produits A et B sont de structure très voisine ou encore lorsque

$$L_A/L_B = m_{AB} = 1$$

Domaine d'applicabilité de la relation de Winstein–Grünwald

Rappelons brièvement les conclusions auxquelles ont abouti les travaux antérieurs:[3–7]

1. La relation de Winstein paraît ne se vérifier exactement que lorsque le dérivé étudié et le dérivé de référence ont des structures très voisines.

2. La vérification exacte de la relation de Winstein dans une grande variété de solvants est un critère de mécanisme S_N1. Les écarts à la droite sont fonction de l'action nucléophile du solvant.

3. La réciproque n'est pas vraie.

4. Dans le cas de mécanismes non limites, pour des dérivés voisins, on obtient

[1] S. Winstein et E. Grünwald, *J. Amer. Chem. Soc.* **70**, 846 (1948).
[2] S. Winstein, E. Grünwald et H. W. Jones, *J. Amer. Chem. Soc.* **73**, 2700 (1951).
[3] Mme Wilputte-Steinert et P. J. C. Fierens, *Bull. Soc. Chim. Belg.* **64**, 277 (1955).
[4] Mme Wilputte-Steinert et P. J. C. Fierens, *Bull. Soc. Chim. Belg.* **64**, 287 (1955).
[5] Mme Wilputte-Steinert et P. J. C. Fierens, *Bull. Soc. Chim. Belg.* **64**, 299 (1955).
[6] Mme Wilputte-Steinert et P. J. C. Fierens, *Bull. Soc. Chim. Belg.* **64**, 308 (1955).
[7] Mme Wilputte-Steinert, P. J. C. Fierens et H. Hannaert, *Bull. Soc. Chim. Belg.* **64**, 628 (1955).

VOL. 6 1959

une droite de Winstein lorsqu'on se borne à l'étude de solvants dont seules varient les proportions en les différents constituants.

B. *Relation de Hammett*

Hammett, reliant la réactivité de la chaîne latérale Y d'un dérivé R–Ph–Y à la nature du substituant R d'un noyau benzénique a proposé l'équation suivante:[8]

$$\log k/k_0 = \sigma\rho \tag{4}$$

où k = vitesse spécifique d'un dérivé substitué en *méta* ou *para* pour une température donnée; k_0 = constante de vitesse correspondant au dérivé non substitué dans le même milieu; σ = paramètre ne dépendant que de la nature du substituant et de sa position défini par l'expression

$$\sigma = \log K/K_0$$

où K et K_0 = constantes d'équilibres des acides benzoïques substitués et non substitué; ρ = paramètre dépendant de la réaction, du solvant et de la température mais indépendant de la nature du substituant.

Cette relation a fait l'objet de nombreuses études, dont Jaffé a présenté une revue critique en 1953.[9]

C. *Relation de Tommila*

Cette relation relie les vitesses de solvolyse des dérivés organiques dans différents solvants, quel que soit le mécanisme réactionnel. Elle fut suggérée à Tommila par Brown et Hudson.[10,11]

Soit

$$\log k = n \log A + C^{te}$$

où k = constante de vitesse à une température donnée, de la solvolyse d'un dérivé organique dans un solvant mixte dont un seul constituant est actif; A = concentration en moles/litre du constituant actif dans le solvant mixte; n = ordre de la réaction par rapport au solvant.

Pour Tommila, n représente le nombre de molécules solvatant le complexe transitoire. A ce nombre de molécules correspond un type de mécanisme réactionnel et toute variation de n implique une variation de mécanisme. Fierens et Berkowitch[12] ont assoupli cette conception en montrant que n est un paramètre caractéristique de la solvatation qui a le maximum de chances de se réaliser et que la constance de n n'est pas une condition nécessaire à l'existence d'un mécanisme constant.

D *Relation entre les équations de Hammett et de Winstein–Grünwald*[7]

Fierens a montré qu'il existe en principe une relation générale entre les vitesses de solvolyse de différents produits dans différents milieux. Soit la relation de Winstein écrite sous la forme:

$$\frac{\log k_{Ax} - \log k_{Ao}}{\log k_{Ox} - \log k_{Oo}} = m_A \tag{6}$$

[8] L. Hammett, *Physical Organic Chemistry*. McGraw-Hill, New York (1940).
[9] H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).
[10] E. Tommila, E. M. Tiilikainen et A. Voipio, *Ann. Acad. Sci. Fenn* A n° 65 (1955).
[11] D. H. Brown et R. F. Hudson, *J. Chem. Soc.* 3352 (1953).
[12] P. J. C. Fierens et J. Berkowitch, *Tetrahedron* **1**, 129 (1957).

où A = dérivé étudié; x = solvant variable; o = solvant de référence; O = dérivé de référence.

La relation de Hammett peut s'exprimer:

$$\frac{\log k_{Xa} - \log k_{Oa}}{\log k_{Xo} - \log k_{Oo}} = \rho_a \tag{7}$$

où a est le solvant étudié; X = le produit variable.

L'expression générale de (6) et (7) est une relation dont la forme analytique est celle d'un paraboloïde hyperbolique dans un système d'axes rectangulaires:

$$\log k_{Xx} = \alpha(\log k_{Xo} - \log k_{Oo})(\log k_{Ox} - \log k_{Oo}) + (\log k_{Xo} - \log k_{Oo}) + (\log k_{Ox} - \log k_{Oo}) + \log k_{Oo} \tag{8}$$

On peut facilement retrouver les équations de Winstein–Grünwald et Hammett à partir de (8) si l'on pose:

$$m_A = \alpha(\log k_{Ao} - \log k_{Oo}) + 1 \tag{9}$$

$$\rho_A = (\log k_{Oa} - \log k_{Oo}) + 1 \tag{10}$$

Si $m_A = 1$, $\alpha = 0$ et le paraboloïde se réduit à un plan dont l'équation est:

$$\log k_{Xx} = (\log k_{Xo} - \log k_{Oo}) + (\log k_{Ox} - \log k_{Oo}) + \log k_{Oo} \tag{11}$$

PARTIE EXPERIMENTALE

A. *Chloruration et Purification des Produits*

Les chlorures d'α-phényléthyle substitués sont liquides et très facilement polymérisables et hydrolysables, même à température ordinaire. De plus, leur température d'ébullition est trop proche de celle de l'alcool correspondant pour pouvoir les purifier efficacement par distillation sous pression réduite. Ces considérations nous ont amenés à réaliser la chloruration des alcools de la manière suivante:

L'alcool, rigoureusement pur, en solution dans du benzène distillé contenant des perlesde chlorure de calcium, est soumis à un barbotage d'HCl sec, à 0°, pendant environ une semaine. Dans ces conditions, la chloruration est complète et seul un faible pourcentage de polymère aisément séparable par distillation a pu se former. Après séchage complet de la solution benzénique sur sulfate de magnésium, l'acide chlorhydrique est soigneusement éliminé à la trompe à eau en évitant les traces d'humidité grâce à des pièges à chlorure de calcium. Le chlorure est ensuite distillé sur courte colonne, sous pression réduite d'azote et sur hydroquinone. Il est conservé à −18° et à l'obscurité.

B. *Synthèse des produits étudiés*

1. *Chlorure d'*α*-(*p*-chlorophényl) éthyle*

L'α-(*p*-chlorophényl) éthanol a été préparé par réaction de Grignard[13] sur le *p*-chloro-benzaldéhyde distillé et recristallisé. Le chlorure correspondant a été obtenu par la méthode générale décrite en A: $n_D^{20} = 1{\cdot}5450$ $T_{éb.} = 65°/0{\cdot}5$ mm.

2. *Chlorure d'*α*-(*m*-méthoxyphényl) éthyle*

La réduction de *m*-nitrobenzaldéhyde par le chlorure stanneux en présence d'acide chlorhydrique permet d'obtenir le complexe stannique du *m*-aminobenzaldéhyde.[14] Son sel de diazonium est hydrolysé par l'eau à l'ébullition.[14] Le *m*-hydroxybenzaldéhyde ainsi obtenu est méthylé au moyen

[13] L. A. Brooks, *J. Amer. Chem. Soc.* **66**, 1295 (1944).
[14] *Organic Synthesis* Coll. Vol. III, p. 453. John Wiley, New York (1955).

de sulfate de méthyle en milieu alcalin.[15] Une réaction de Grignard[16] permet ensuite d'obtenir l'α-(*m*-méthoxyphényl) éthanol. Le chlorure d' α-(*m*-méthoxyphényl) éthyle a été obtenu par la méthode décrite en A. $n_D^{20} = 1{\cdot}5341$ $T_{éb.} = 75°/0{\cdot}08$ mm.

3. *Chlorure d'*α*-*(p-*fluorophényl) éthyle*

Nous avons obtenu la *p*-fluoroacétophénone par réaction de Friedel–Crafts sur le fluorobenzène.[16] Cette cétone a été réduite par la réaction de Meerwein–Pondorff.[17]

Le chlorure d'α-(*p*-fluorophényl) éthyle a ensuite été obtenu par la méthode décrite en A. Ce dérivé nouveau n'a pu être envoyé à l'analyse étant donné sa grande réactivité. Seul, le chlore a pu être déterminé. $T_{éb.} = 43°/0{\cdot}5$ mm; $n_D^{20} = 1{\cdot}5044$; Cl % trouvé 22·5; Cl % calculé 22·4.

4. *Chlorure d'*α*-*(p-*méthylphényl) éthyle*

La *p*-méthylacétophénone a été préparée par réaction de Friedel-Crafts entre le toluène et l'anhydride acétique.[18] L'α-(*p*-méthylphényl) éthanol a été obtenu de la même manière que le dérivé fluoré correspondant.[17] Cet alcool a ensuite été chloré par la méthode décrite en A. $n_D^{20} = 1{\cdot}5232$ $T_{éb.} = 61°/1{\cdot}5$ mm.

5. *Chlorure d'*α*-*(m-*méthylphényl) éthyle*

Le *m*-bromotoluène a été synthétisé à partir de *m*-toluidine[15] par réaction de Sandmeyer. L'addition d'acétaldéhyde au bromure de *m*-tolylmagnésium a permis d'obtenir aisément l'α-(*m*-méthylphényl) éthanol.[19] Le chlorure d'α-(*m*-méthylphényl) éthyle a ensuite été obtenu par chloruration au moyen d'HCl. $n_D^{20} = 1{\cdot}5262$ $T_{éb.} = 69–73°/2{\cdot}5$ mm.

6. *Chlorure d'*α*-*(m-*chlorophényl) éthyle*

Le *m*-chlorobenzaldéhyde a été préparé par réduction du *m*-nitrobenzaldéhyde au moyen de chlorure stanneux, suivi d'une réaction de Sandmeyer en présence de CuCl.[20]

L'alcool secondaire correspondant a été obtenu par réaction de Grignard.[13] Ce dérivé a ensuite été chloré par la méthode décrite en A. $n_D^{20} = 1{\cdot}5441$ $T_{éb.} = 65°/2$ mm.

C. *Purification des solvants*

Eau: nous avons utilisé de l'eau de conductivité pour nos mesures.

Dioxanne: le dioxanne, chauffé à reflux sur potasse jusqu'à élimination complète des résines, est ensuite séché et distillé sur sodium au moyen d'une colonne Widmer. $n_D^{20} = 1{\cdot}4232$ $T_{éb.} = 101{\cdot}3°/760$ mm.

Acide formique: la quantité d'eau contenue dans l'acide formique Merck "pro analysi" a été mesurée par la température critique de solubilité.[21]

D. *Résultats cinétiques*

1. *Technique opératoire*

Le degré d'avancement des réactions a été mesuré au moyen d'une méthode conductométrique[22] et d'étalonnages préalablement établis.[23–25] Rappelons que pour les milieux dont la teneur est égale ou supérieure à 50‰, la conductivité est proportionnelle à la concentration en HCl. Ces milieux permettent donc de travailler sans étalonnages à de très faibles concentrations, la concentration initiale en produit étant déterminée par conductivité à 100% de réaction.

[15] *Organic Synthesis* Coll. Vol. III, p. 564. John Wiley, New York (1955).
[16] *Organic Synthesis* Coll. Vol. I. p. 109. John Wiley, New York (1948).
[17] C. S. Marvel et G. L. Schertz, *J. Amer. Chem. Soc.* **65**, 2054 (1943).
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2. *Détermination des constantes de vitesse spécifique*

Les réactions étant monomoléculaires, les constantes de vitesse ont été déterminées par l'équation:

$$k = \frac{2{\cdot}303}{t} \log \frac{a}{a - x} \tag{12}$$

a = concentration initiale en halogénure exprimée en moles/litre; x = concentration en HCl à chaque instant au cours de la réaction; t = temps exprimé en secondes.

Notons que lorsqu'on emploie la méthode à la goutte pour les milieux riches en eau, l'équation permettant de déterminer k peut s'écrire

$$k = \frac{2{\cdot}303}{t} \log \frac{C_{\text{équilibre}}}{C_{\text{équilibre}} - C_t} \tag{13}$$

où $C_{\text{équilibre}}$ = conductivité à 100% de réaction; C_t = conductivité au temps t.

Nos résultats expérimentaux ont été réunis dans les tableaux 1 à 12 où: a représente la concentration initiale en halogénure exprimée en moles litre; n le nombre de mesures effectuées; σ les écarts types calculés suivant une méthode mise au point par Halleux, Kruys et Huybrechts.[27]

Le Tableau 13 renferme les résultats cinétiques relatifs au chlorure d'α-phényléthyle.[4]

TABLEAU 1. SOLVOLYSES DU CHLORURE D'α(*m*-MÉTHYLPHÉNYL) ETHYLE

Solvant			E kcal/mole	$\sigma(E)$	log PZ	σ(log PZ)	log $k_{25°}$
Eau	Dioxanne	Ac. form.					
20·5%	79·5%		23·13	0·05	10·96	0·03	−6·00
49·3	50·7		21·64	0·02	12·07	0·02	−3·80
66·6	33·3		—	—	—	—	−2·61
5·8	60·2	34·0%	20·63	0·06	10·06	0·04	−5·07
6·1	39·8	54·1	21·90	0·03	12·10	0·02	−3·96
5·3	25·8	69·7	—	—	—	—	−3·25

TABLEAU 2. SOLVOLYSES DU CHLORURE D'α-(*m*-MÉTHOXYPHÉNYL) ÉTHYLE

Solvant			E kcal/mole	$\sigma(E)$	log PZ	σ(log PZ)	log $k_{25°}$
Eau	Dioxanne	Ac. form.					
20·5%	79·5%		22·90	0·05	10·22	0·03	−6·57
49·3	50·7		21·17	0·03	11·01	0·02	−4·51
66·6	33·3		22·90	0·1	13·40	0·09	−3·39
5·8	60·2	34·0%	21·91	0·04	10·38	0·03	−5·69
6·1	39·8	54·1	21·57	0·03	11·23	0·02	−4·59
5·3	25·8	69·7	22·59	0·04	12·69	0·03	−3·94

DISCUSSION

A. *Relation de Winstein–Grünwald*

Fierens[7] a montré que la relation de Winstein–Grünwald appliquée à la solvolyse du chlorure d'α-phényléthyle, en employant le chlorure de butyle tertiaire comme dérivé de référence, est loin d'être vérifiée exactement.

[27] A. Halleux, P. Kruys et S. Huybrechts, *Bull. Soc. Chim. Belg.* **64**, 191 (1955).

TABLEAU 3. SOLVOLYSES DU CHLORURE D'α-(*m*-CHLOROPHÉNYL) ÉTHYLE

Solvant			E kcal/mole	$\sigma(E)$	log PZ	σ(log PZ)	log $k_{25°}$
Eau	Dioxanne	Ac. form.					
20·5%	79·5%		22·14	0·06	8·35	0·03	−7·88
49·3	50·7		21·97	0·07	9·98	0·04	−6·13
66·6	33·3		20·96	0·01	10·36	0·05	−5·01
5·8	60·2	34·0%	23·89	0·07	10·02	0·009	−7·50
6·1	39·8	54·1	23·73	0·05	10·88	0·03	−6·52
5·3	25·8	69·7	23·43	0·03	11·28	0·02	−5·90

TABLEAU 4. SOLVOLYSES DU CHLORURE D'α-(*p*-CHLOROPHÉNYL) ÉTHYLE

Solvant			E kcal/mole	$\sigma(E)$	log PZ	σ(log PZ)	log $k_{25°}$
Eau	Dioxanne	Ac. form.					
20·5%	79·5%		22·2	0·05	9·76	0·01	−6·53
49·3	50·7		20·68	0·01	10·51	0·01	−4·65
66·6	33·3		20·79	0·02	11·80	0·02	−3·44
5·8	60·2	34·0%	22·56	0·05	10·53	0·02	−6·00
6·1	39·8	54·1	22·70	0·02	11·66	0·01	−4·98
5·3	25·8	69·7	23·00	0·02	12·58	0·01	−4·28

TABLEAU 5. SOLVOLYSES DU CHLORURE D'α-(*p*-MÉTHYLPHÉNYL) ÉTHYLE

Solvant			E kcal/mole	$\sigma(E)$	log PZ	σ(log PZ)	log $k_{25°}$
Eau	Dioxanne	Ac. form.					
20·5%	79·5%		20·01	0·10	10·06	0·06	−4·61
5·8	60·2	34·0%	19·75	0·02	10·68	0·02	−3·80
6·1	39·8	54·1	—	—	—	—	−2·30

TABLEAU 6. SOLVOLYSES DU CHLORURE D'α-(*p*-FLUOROPHÉNYL) ÉTHYLE

Solvant			E kcal/mole	$\sigma(E)$	log PZ	σ(log PZ)	log $k_{25°}$
Eau	Dioxanne	Ac. form.					
20·5%	79·5%		21·17	0·03	9·70	0·02	−5·82
49·3	50·7		21·53	0·05	12·20	0·03	−3·53
66·6	33·3		20·93	0·01	13·03	0·01	−2·32
5·8	60·2	34·0%	21·31	0·02	10·48	0·01	−5·14
6·1	39·8	54·1	21·93	0·03	12·04	0·02	−4·03
5·3	25·8	69·7	22·36	0·03	13·09	0·02	−3·31

VOL. 6 1959

TABLEAU 7. SOLVOLYSES DU CHLORURE D'α-(*p*-CHLOROPHÉNYL) ÉTHYLE

T	*n*	$a \cdot 10^3$ (mole/litre)	*k* (sec^{-1})	*T*	*n*	$a \cdot 10^3$ (mole/litre)	*k* (sec^{-1})
Milieu 1	eau 20·5% dioxanne 79·5%			*Milieu* 4	eau 5·8% dioxanne 60·2% ac. form. 34·0%		
79°3	16	2·584	$9{\cdot}50 \times 10^{-5}$	50°8	20	1·778	$1{\cdot}92 \times 10^{-5}$
90°1	19	2·149	$2{\cdot}47 \times 10^{-4}$	60°	19	1·663	$5{\cdot}41 \times 10^{-5}$
99°9	19	2·125	$5{\cdot}44 \times 10^{-4}$	74°5	16	1·843	$2{\cdot}20 \times 10^{-4}$
104°1	20	2·116	$7{\cdot}66 \times 10^{-4}$	89°7	19	1·617	$8{\cdot}51 \times 10^{-4}$
Milieu 2	eau 49·3% dioxanne 50·7%			*Milieu* 5	eau 6·1% dioxanne 39·8% ac. form. 54·1%		
25°	18	1·583	$2{\cdot}21 \times 10^{-4}$	25°	23	1·840	$1{\cdot}05 \times 10^{-3}$
36°2	20	2·179	$7{\cdot}76 \times 10^{-4}$	31°	21	2·007	$2{\cdot}20 \times 10^{-3}$
45°	19	1·708	$1{\cdot}95 \times 10^{-3}$	50°8	20	1·795	$2{\cdot}25 \times 10^{-4}$
60°	13	2·140	$8{\cdot}68 \times 10^{-3}$	60°	21	1·780	$5{\cdot}80 \times 10^{-4}$
Milieu 3	eau 66·6% dioxanne 33·3%			*Milieu* 6	eau 5·3% dioxanne 25·8% ac. form. 69·7%		
15°	20	—	$1{\cdot}06 \times 10^{-4}$	25°	18	1·239	$5{\cdot}06 \times 10^{-5}$
25°	18	—	$3{\cdot}56 \times 10^{-4}$	31°	16	1·448	$1{\cdot}11 \times 10^{-4}$
31°	20	—	$7{\cdot}13 \times 10^{-4}$	33°9	17	1·436	$3{\cdot}29 \times 10^{-4}$
45°	18	—	$3{\cdot}26 \times 10^{-3}$	50°9	22	1·421	$1{\cdot}09 \times 10^{-3}$

L'étude des bases théoriques de cette relation semble prouver que sa vérification rigoureuse exige une grande similitude au voisinage du centre réactionnel entre les deux produits que l'on compare. C'est pourquoi nous avons dressé les graphiques de Winstein, correspondant aux dérivés substitués étudiés, en employant le dérivé non substitué comme substance de référence (Figs. 1 à 6). Un examen rapide de ces graphiques montre que:

(a) les écarts aux droites les plus probables obtenues sont très faibles pour les dérivés *p*-Cl, *m*-Cl et *p*-F substitués (Figs. 1, 4 et 6).

(b) pour les substituants *m*-OCH_3 et *m*-CH_3 (Figs. 2 et 3), les graphiques de Winstein sont constitués par deux droites très voisines, chacune correspondant aux solvolyses dans un même type de solvants mixtes. L'écart entre ces deux droites est d'environ 0·2 unité de log *k* pour le dérivé *m*-OCH_3 et de 0·1 unité de log *k* pour le substituant *m*-CH_3.

(c) le dérivé *p*-CH_3 (Fig. 5) réagit très rapidement avec les solvants étudiés, les vitesses de solvolyse n'ont pu être étudiées avec une bonne précision que dans les

TABLEAU 8. SOLVOLYSES DU CHLORURE D'α-(*p*-MÉTHYLPHÉNYL) ÉTHYLE

T	n	$a \cdot 10^2$ (mole/litre)	k (sec^{-1})
Milieu 1 eau 20·5% dioxanne 79·5%			
40°	20	2·354	$1{\cdot}16 \times 10^{-4}$
40°	20	2·354	$1{\cdot}18 \times 10^{-4}$
59·9	20	1·993	$8{\cdot}51 \times 10^{-4}$
70°	20	2·398	$1{\cdot}89 \times 10^{-3}$
Milieu 4 eau 5·8% dioxanne 60·2% ac. form. 34·0%			
15°	14	1·342	$4{\cdot}49 \times 10^{-5}$
25°	18	1·328	$1{\cdot}57 \times 10^{-4}$
31°	18	1·320	$3{\cdot}02 \times 10^{-4}$
10°	16	1·403	$7{\cdot}61 \times 10^{-4}$
Milieu 5 eau 6·1% dioxanne 39·8% ac. form. 54·1%			
25°	—	—	5×10^{-3}

deux milieux les moins actifs. Il est donc impossible de tirer des conclusions des résultats concernant ce produit.

(d) les coefficients angulaires des droites de Winstein sont tous très voisins de l'unité; ceci confirme l'équation:

$$m_{AB} = L_A/L_B$$

où m_{AB} est le coefficient angulaire de la droite, L_A et L_B les paramètres de structure ne dépendant que des produits A et B (Tableau 14).

Effet nucléophile du solvant

Un examen détaillé des graphiques montre qu'il existe des écarts à la droite de Winstein, correspondant aux dérivés ayant les σ les plus positifs, c'est-à-dire les substituants les plus capteurs (*m*-Cl, *m*-OCH_3, *p*-Cl) dans le milieu le moins ionisant (79·5% dioxanne–20·5% d'eau). Ces constantes de vitesse mesurées sont plus grandes que celles prédites par la relation de Winstein; ceci correspond à une légère action nucléophile du solvant au niveau du complexe transitoire.

Effets des substituants m-OCH_3 *et* m-CH_3

Il est difficile de justifier l'existence des deux droites obtenues pour les substituants *m*-OCH_3 et *m*-CH_3. On peut néanmoins affirmer que ces écarts ne sont pas dus à la

TABLEAU 9. SOLVOLYSES DU CHLORURE D'α(*m*-MÉTHOXYPHÉNYL) ÉTHYLE

T	n	$a \cdot 10^3$ (mole/litre)	k (sec^{-1})	T	n	$a \cdot 10^3$ (mole/litre)	k (sec^{-1})
Milieu 1 eau 20·5% dioxanne 79·5%				*Milieu* 4 eau 5·8% dioxanne 60·2% ac. form. 34·0%			
60°	19	2·322	$1{\cdot}52 \times 10^{-5}$	40°1	21	1·590	$1{\cdot}25 \times 10^{-5}$
70°2	20	2·299	$4{\cdot}35 \times 10^{-5}$	51°2	16	1·573	$4{\cdot}05 \times 10^{-5}$
79°9	21	2·279	$1{\cdot}01 \times 10^{-4}$	60°2	21	1·560	$1{\cdot}00 \times 10^{-4}$
89°9	21	2·002	$2{\cdot}67 \times 10^{-4}$	74°5	22	1·537	$4{\cdot}15 \times 10^{-4}$
Milieu 2 eau 49·3% dioxanne 50·7%				*Milieu* 5 eau 6·1% dioxanne 39·8% ac. form. 54·1%			
16°8	16	3·030	$1{\cdot}12 \times 10^{-5}$	25°	20	1·619	$2{\cdot}53 \times 10^{-5}$
25°	15	3·013	$3{\cdot}08 \times 10^{-5}$	31°1	18	1·646	$5{\cdot}19 \times 10^{-5}$
36°2	17	2·522	$1{\cdot}17 \times 10^{-4}$	40°1	17	1·632	$1{\cdot}50 \times 10^{-4}$
45°2	21	2·506	$2{\cdot}34 \times 10^{-4}$	51°2	20	1·615	$1{\cdot}74 \times 10^{-4}$
Milieu 3 eau 66·6% dioxanne 33·3%				*Milieu* 6 eau 5·3% dioxanne 25·8% ac. form. 69·7%			
12°9	10	—	$7{\cdot}80 \times 10^{-5}$	25°	18	1·482	$1{\cdot}14 \times 10^{-4}$
13°	10	—	$8{\cdot}34 \times 10^{-5}$	25°1	17	1·205	$1{\cdot}14 \times 10^{-4}$
25°	10	—	$3{\cdot}70 \times 10^{-4}$	40°1	16	1·228	$7{\cdot}04 \times 10^{-4}$
25°	10	—	$3{\cdot}97 \times 10^{-4}$	51°2	15	1·210	$2{\cdot}52 \times 10^{-3}$
25°	10	—	$4{\cdot}06 \times 10^{-4}$				
35°8	10	—	$1{\cdot}69 \times 10^{-3}$				
40°	10	—	$2{\cdot}44 \times 10^{-3}$				

présence de sel d'oxonium. En effet, Wiles[28] a montré que les sels d'oxonium de dérivés benzéniques substitués par un groupe méthoxy ne se forment qu'en présence d'acide fort et concentré. L'existence de sels d'oxonium dans les milieux ternaires est également impossible; en effet, le substituant $\overset{+}{O}CH_3$ est fortement capteur par rapport à-OCH_3. Or, on constate que les solvolyses dans ces milieux sont plus rapides que dans les mélanges binaires correspondant au même pouvoir ionisant.

Conclusion

(1°) La relation de Winstein–Grünwald est vérifiée d'une manière très précise pour les dérivés *p*-fluoro, *p*-chloro et *m*-chloro dans une grande variété de solvants mixtes. Ceci est dû au fait:

(a) que le mécanisme de réaction est une substitution nucléophile monomoléculaire

[28] L. A. Wiles, *Chem. Rev.* **56**, 329 (1956).

TABLEAU 10. SOLVOLYSES DU CHLORURE D'α-(*m*-CHLOROPHÉNYL) ÉTHYLE

T	n	$a \times 10^3$ (mole/litre)	k (sec^{-1})	T	n	$a \times 10^3$ (mole/litre)	k (sec^{-1})
Milieu 1	eau 20·5% dioxanne 79·5%			*Milieu* 4	eau 5·8% dioxanne 60·2% ac. form. 34·0%		
79°1	20	2·807	$4{\cdot}13 \times 10^{-6}$	60°	16	1·640	$2{\cdot}21 \times 10^{-6}$
98°9	17	1·674	$2{\cdot}14 \times 10^{-5}$	74°5	19	1·505	$9{\cdot}48 \times 10^{-6}$
103°8	20	1·666	$3{\cdot}25 \times 10^{-5}$	74°5	15	1·618	$1{\cdot}00 \times 10^{-5}$
110°	20	1·948	$5{\cdot}25 \times 10^{-5}$	90°	19	1·483	$4{\cdot}32 \times 10^{-5}$
Milieu 2	eau 49·3% dioxanne 50·7%			*Milieu* 5	eau 6·1% dioxanne 39·8% ac. form. 54·1%		
45°	19	2·248	$7{\cdot}15 \times 10^{-6}$	60°	20	1·444	$1{\cdot}97 \times 10^{-5}$
60°3	18	1·906	$3{\cdot}88 \times 10^{-5}$	74°5	14	1·730	$8{\cdot}99 \times 10^{-5}$
82°8	20	2·180	$2{\cdot}95 \times 10^{-4}$	83°	18	1·414	$2{\cdot}07 \times 10^{-4}$
82°8	20	1·777	$3{\cdot}03 \times 10^{-4}$	90°	20	1·405	$3{\cdot}77 \times 10^{-4}$
Milieu 3	eau 66·6% dioxanne 33·3%			*Milieu* 6	eau 5·3% dioxanne 25·8% ac. form. 69·7%		
25°	12	—	$9{\cdot}46 \times 10^{-6}$	51°	20	1·444	$2{\cdot}97 \times 10^{-5}$
25°	13	—	$9{\cdot}66 \times 10^{-6}$	60°	20	1·525	$7{\cdot}84 \times 10^{-5}$
45°3	19	—	$9{\cdot}23 \times 10^{-5}$	74°9	20	1·414	$3{\cdot}72 \times 10^{-4}$
59°7	20	—	$3{\cdot}86 \times 10^{-4}$	83°	19	1·425	$7{\cdot}72 \times 10^{-4}$

(sauf en ce qui concerne les dérivés *m*- et *p*-chloro dans le milieu 79·5% dioxanne–20·5% eau);

(b) qu'il n'existe pas d'interaction spécifique de chacun des deux types de solvant avec le substituant;

(c) que du point de vue stérique, les sites réactionnels des dérivés étudiés et du dérivé de référence sont identiques.

(2°) En ce qui concerne les dérivés *m*-méthoxy- et *m*-méthyle substitués, la présence de deux droites parallèles voisines peut être attribuée à diverses interactions spécifiques de chaque type de solvant avec le substituant. Le mécanisme est néanmoins S_N1, sauf, vraisemblablement pour le dérivé *m*-OCH_3 dans le milieu 79·5% dioxanne–20·5% eau.

B. *Relation de Tommila*

Nous avons appliqué la relation de Tommila aux constantes de vitesse mesurées dans les mélanges binaires.

Soit
$$\log k = n \log (H_2O) + Cte \qquad (14)$$

TABLEAU 11. SOLVOLYSES DU CHLORURE D'α-(*p*-FLUOROPHÉNYL)ÉTHYLE

T	n	$a \times 10^3$ (mole/litre)	k (sec^{-1})	T	n	$a \times 10^3$ (mole/litre)	k (sec^{-1})
Milieu 1	eau 20·5% dioxanne 79·5%			*Milieu* 4	eau 5·8% dioxanne 60·2% ac. form. 34·0%		
45°	19	2·473	$1·41 \times 10^{-5}$	31°	17	1·984	$1·45 \times 10^{-5}$
45°	19	2·473	$1·43 \times 10^{-5}$	31°	17	1·984	$1·45 \times 10^{-5}$
60°3	19	2·438	$6·50 \times 10^{-5}$	40°2	16	1·823	$4·08 \times 10^{-5}$
78°9	20	2·393	$3·60 \times 10^{-4}$	60°	22	1·984	$3·13 \times 10^{-4}$
Milieu 2	eau 49·3% dioxanne 50·7%			*Milieu* 5	eau 6·1% dioxanne 39·8% ac. form. 54·1%		
12°	18	2·550	$4·83 \times 10^{-5}$	25°2	17	1·356	$9·38 \times 10^{-5}$
17°	17	2·541	$9·33 \times 10^{-5}$	25°2	17	1·356	$9·40 \times 10^{-5}$
25°	20	2·527	$2·62 \times 10^{-4}$	40°2	20	1·343	$5·41 \times 10^{-4}$
36°	17	2·506	$9·15 \times 10^{-5}$	51°	19	1·329	$1·81 \times 10^{-3}$
Milieu 3	eau 66·6% dioxanne 33·3%			*Milieu* 6	eau 5·3% dioxanne 25·8% ac. form. 69·7%		
0°	15	—	$1·87 \times 10^{-4}$	15°	17	1·341	$1·32 \times 10^{-4}$
0°	13	—	$1·88 \times 10^{-4}$	25°3	16	1·329	$2·00 \times 10^{-4}$
0°	14	—	$1·86 \times 10^{-4}$	30°9	18	1·321	$1·00 \times 10^{-3}$
15°	23	—	$1·40 \times 10^{-3}$	40°	18	1·310	$3·00 \times 10^{-3}$
15°	20	—	$1·39 \times 10^{-3}$				

Portant en abcisse les logarithmes des titres molaires en eau, et en ordonnée les logarithmes des constantes spécifiques, à 25°, nous avons obtenu le graphique 7 (Tableau 15). Nous y remarquons:

(1°) que la pente des tronçons de droite obtenus pour le dérivé non substitué dans les milieux les plus riches en eau (66·6% eau–80% eau–100% eau) est pratiquement constante et voisine de 9·7.

(2°) que les tronçons de droite joignant les points correspondant aux deux milieux contenant 50% eau et 66·6% eau, sont parallèles pour l'ensemble des produits étudiés.

(3°) que la pente des segments de droite joignant les points correspondant aux deux milieux les moins riches en eau est beaucoup plus faible que celle correspondant aux milieux les plus riches en eau. Cette pente est voisine de 6·0. Trois de ces segments sont parallèles; ils correspondent aux dérivés *p*-fluoro, *m*-méthyle et non substitués qui réagissent par un mécanisme S_N1 dans tous les solvants étudiés. Les autres dérivés pour lesquels les droites de Winstein avaient révélé l'existence d'une contribution du bond-making dans le milieu 20·5% eau, ont une pente plus faible que les précédentes.

TABLEAU 12. SOLVOLYSES DU CHLORURE D'α-(*m*-MÉTHYLPHÉNYL) ÉTHYLE

T	n	$a \times 10^2$ (mole/litre)	k (sec^{-1})	T	n	$a \times 10^2$ (mole/litre)	k (sec^{-1})
Milieu 1	eau 20·5% dioxanne 79·5%			*Milieu* 4	eau 5·8% dioxanne 60·2% ac. form. 34·0%		
45°	20	2·335	$1·14 \times 10^{-5}$	25°	20	1·579	$8·53 \times 10^{-6}$
50·4	20	1·953	$2·12 \times 10^{-5}$	31°	20	1·851	$1·73 \times 10^{-5}$
60°	20	2·057	$6·04 \times 10^{-5}$	40°	20	1·834	$4·44 \times 10^{-5}$
69·8	20	2·920	$1·56 \times 10^{-4}$	50·9	20	1·541	$1·43 \times 10^{-4}$
Milieu 2	eau 49·3% dioxanne 50·7%			*Milieu* 5	eau 6·1% dioxanne 39·8% ac. form. 54·1%		
12°	20	1·978	$2·97 \times 10^{-5}$	14·9	20	1·707	$3·01 \times 10^{-5}$
17°	20	2·179	$5·71 \times 10^{-5}$	25°	20	1·541	$1·08 \times 10^{-4}$
25·3	19	2·167	$1·65 \times 10^{-4}$	31°	20	1·681	$2·34 \times 10^{-4}$
36°	13	1·945	$5·76 \times 10^{-4}$	40°	19	1·675	$6·43 \times 10^{-4}$
Milieu 3	eau 66·6% dioxanne 33·3%			*Milieu* 6	eau 5·3% dioxanne 25·8% ac. form. 69·7%		
25·1	16	—	$2·43 \times 10^{-5}$	25·1	20	1·395	$5·64 \times 10^{-4}$
25·1	13	—	$2·47 \times 10^{-5}$	25°	17	1·535	$5·65 \times 10^{-4}$

La constance *de n* n'est donc pas une condition nécessaire à l'existence d'un seul mécanisme réactionnel. Toute attaque covalente du solvant se traduit néanmoins par un abaissement de n supérieur à celui qui se produit à mécanisme constant.

C. *La relation de Hammett*

1. *Etude des énergies d'activation et des logarithmes des facteurs de fréquence*

Il est généralement admis que l'une des deux conditions suivantes est nécessaire à la vérification de l'équation de Hammett:

(a) l'entropie d'activation est constante pour tous les termes de la série étudiée. Dans ce cas: $\rho T = Cte$[29]

(b) les enthalpies d'activation sont fonction linéaire de l'entropie d'activation.[8–30]

L'examen de nos résultats expérimentaux nous permet de constater que les *PZ* sont constants pour les dérivés *para* substitués dans les milieux eau 20·5%–dioxanne 79·5% et eau 5·8%–acide formique 34%–dioxanne 60·2%. Dans ces milieux, les valeurs de l'énergie d'activation sont fonction croissante de la valeur de σ.

Les phénomènes se présentent d'une manière très différente pour les dérivés

[29] J. Vène et J. Tirouflet, *Bull. Soc. Chim. Fr.* 220–226 (1954).
[30] J. E. Leffler, *J. Org. Chem.* **20**, 1202 (1955).

VOL. 6 1959

TABLEAU 13. SOLVOLYSES DU CHLORURE D'α-PHÉNYLÉTHYLE

Solvant			E kcal/m	log PZ	log k 25°
Eau	Dioxanne	Ac. form.			
20·5%	79·5%	—	22·3	10·02	−6·36
49·3%	50·7%	—	21·2	11·43	−4·15
66·67%	33·33%	—	20·0	11·74	−2·96
79·5%	20·5%	—	19·8	12·37	−2·18
100 %	—	—	(20)	(13·34)	−1·33
5·8%	60·2%	34·0%	22·7	11·07	−5·59
6·1%	39·8%	54·1%	22·5	12·01	−4·51
5·3%	25·0 %	69·7%	22·8	12·96	−3·79

TABLEAU 14. SOLVOLYSES DE CHLORURES D'α-PHÉNYLÉTHYLES SUBSTITUÉS. ETUDE DU COEFFICIENT ANGULAIRE DES DROITES DE WINSTEIN-GRÜNWALD

Dérivés étudiés	m
m-Cl	0·90
m-CH_3	1
	0·97
m-OCH_3	0·99
	0·97
p-Cl	0·97
p-F	1·03

TABLEAU 15. SOLVOLYSES DE CHLORURES D'α-PHÉNYLÉTHYLES SUBSTITUÉS
ETUDE DU LOGARITHME DES CONSTANTES DE VITESSE EN FONCTION DU TITRE MOLAIRE EN EAU

			−log $k_{25°}$					
% Eau	$[H_2O]_{25°}$ mole/litre	log $[H_2O]$						
				Cl	F	Cl	OCH_3	CH_3
20·5	11·48	1·060	6·36	6·53	5·82	7·88	6·57	6·00
49·3	27·86	1·445	4·15	4·65	3·59	6·13	4·51	3·80
66·6	38·16	1·581	2·96	3·44	2·32	5·01	3·39	2·61
79·5	44·60	1·649	2·18	—	—	—	—	—
100	55·43	1·744	1·33	—	—	—	—	—

TABLEAU 16. SOLVOLYSES DE CHLORURES D'α-PHÉNYLÉTHYLES MÉTA SUBSTITUÉS
Etude du coefficient angulaire des droites de Hammett en fonction du milieu étudié et détermination de la valeur de la constante du substituant m-OCH_3 dans chacun de ces milieux.

Milieu			$\rho_{25°}$	$\sigma_{m\text{-}OCH_3}$
Eau	Dioxanne	Ac. form.		
20·5%	79·5%	—	4·3*	0·06 ± 0·01
49·3%	50·7%	—	5·3	0·07
66·6%	33·3%	—	5·3	0·07
5·8%	60·2%	34·0%	5·4	0·03
6·1%	39·8%	54·1%	5·8	0·03
5·3%	25·8%	69·7%	—	0·03

* Rappelons que dans le milieu 20·5% eau–79·5% dioxanne, le mécanisme de solvolyse du dérivé m-Cl substitué n'est pas SN_1 pur.

m-substitués. Dans les milieux binaires 20·5% eau–79·5% dioxanne et 49·3% eau–50·7% dioxanne, la variation d'énergie est très faible d'un produit à l'autre alors que les log *PZ* varient de plus de deux unités.

La dispersion des log *PZ* est plus faible (0·8 unité) dans le milieu ternaire 60·2% dioxanne–5·8% eau–34% acide formique.

Dans tous les autres milieux, les valeurs de *E* et de log *PZ* se répartissent d'une manière quelconque rendant impossible toute interprétation même qualitative des résultats obtenus.

2. *Etude de la variation du logarithme de la constante de vitesse en fonction de* ρ

Nous avons dressé tout d'abord un graphique de Hammett contenant les résultats des solvolyses de l'ensemble des dérivés étudiés, dans le milieu 60·2% dioxanne–34% acide formique–5·8% eau (Fig. 8). La longueur du trait horizontal représente l'erreur probable sur σ; l'erreur sur log k est négligeable. L'ensemble des traits obtenus se répartit très grossièrement sur une droite. Cependant, si on néglige le dérivé méthoxy substitué pour lequel le σ est par trop imprécis, on constate que les dérivés *para* d'une part, et les dérivés *méta* et non substitués d'autre part, se placent sur une droite avec une précision beaucoup meilleure.

Ceci nous a conduits à faire le même type de graphique pour les dérivés *méta*- et non substitués dans chaque solvant, puis pour les dérivés *para* dans les milieux étudiés (Figs. 9, 10 et 11). Les droites obtenues pour les dérivés *m*-Cl, *m*-CH_3 et H sont précises dans tous milieux et ont des coefficients angulaires voisins, à l'exception de celle correspondant au milieu 79·5% dioxanne pour lequel une contribution du bond-making a été mise en évidence.

A l'aide de nos graphiques, nous avons déterminé la valeur de la constante du substituant *m*-OCH_3 correspondant à ce type de réaction dans chaque milieu. Les valeurs obtenues sont très voisines l'une de l'autre. Le coefficient angulaire des droites est négatif puisque les substituants capteurs d'électrons défavorisent les substitutions nucléophiles monomoléculaires; les pentes sont approximativement

égales dans les différents solvants. Le Tableau 16 renferme les valeurs de σ_{m-OCH_3} et de ρ correspondant à chaque milieu.

En ce qui concerne les dérivés *para* substitués les droites obtenues sont aussi précises que les précédentes. Les valeurs de ρ sont égales entre elles si l'on tient compte du fait que la formation de la nouvelle liaison intervient au niveau du complexe transitoire pour le dérivé *p*-Cl dans le milieu 79·5% dioxanne–20·5% eau et que l'on remplace la valeur de log k mesurée par celle extrapolée à l'aide du graphique de Winstein–Grünwald.

L'existence de deux droites de Hammett, l'une correspondant aux dérivés *para*-substitués, l'autre aux dérivés *meta* et non substitué, a été mise en évidence par d'autres[8] pour les substitutions nucléophiles monomoléculaires en chaîne latérale. Des écarts importants à la droite de Hammett ont été observés de même pour les substitutions électrophiles et pour les réactions des amines et des phénols substitués par des capteurs forts. Ceci est parfaitement explicable si l'on considère que σ est proportionnel à la différence d'enthalpie entre

I II

Cette différence d'enthalpie entre I et II dépend essentiellement de la différence des effets inductifs et mésomères se manifestant entre I et II. Les σ correspondent donc à une séquence déterminée de différences d'enthalpie mais il est évident qu'en changeant la chaîne latérale ou la réaction, on modifie les possibilités de conjugaison et la densité électronique au voisinage du centre réactionnel. Ceci conduit à une séquence de différences d'enthalpie qui peut ne pas être proportionnelle à celle des sigmas.

3. *Effet de la nature du solvant sur la valeur de la constante de réaction*

La constance de ρ dans les différents milieux est en désaccord avec les théories de Jaffe et de Hammett.

Il est pourtant aisé de montrer qu'il doit en être ainsi lorsque les équations de Hammett et de Winstein–Grünwald sont satisfaites simultanément pour la série de produits et de solvants étudiés.

En effet, dans ce cas:

$$\log k_{Xz} = \alpha(\log k_{Xo} - \log k_{Oo})(\log k_{Oz} - \log k_{Oo}) + (\log k_{Xo} - \log k_{Oo}) + (\log k_{Oz} - \log k_{Oo}) + \log k_{Oo} \quad (8)$$

et
$$\alpha = \frac{m_A - 1}{\log k_{Ao} - \log k_{Oo}} = \frac{\rho a - 1}{\log k_{Oa} - \log k_{Oo}} \quad (15)$$

Rappelons que $m = 1$ pour tous les dérivés étudiés et pour l'ensemble des solvants. Nous avons donc aussi: $\alpha = 0$ et $\rho_a = 1$.

Rappelons que:
$$\rho_a = \frac{\log k_{Xa} - \log k_{Oa}}{\log k_{Xo} - \log k_{Oo}} \quad (16)$$

Or, chaque fois que la relation de Hammett s'applique à une série de dérivés substitués et que le mécanisme est limite, soit S_N1, soit S_N2, la relation de Winstein sera vérifiée avec une bonne approximation si l'on choisit le dérivé non substitué comme substance de référence; la constante de réaction ou encore la sensibilité de la réaction à un changement de substituant, sera donc indépendante de la nature du solvant dans chacun de ces cas.

4. *Effet d'un changement de mécanisme sur la valeur de la constante de réaction*

Nous avons montré que les coefficients angulaires des droites de Hammett correspondant au milieu 79·5% dioxanne où une action covalente du solvant se manifeste au niveau du complexe transitoire pour les dérivés *m*-Cl et *p*-Cl, sont plus faibles que ceux correspondant aux autres milieux.

L'effet d'un changement de mécanisme sur la valeur de ρ a été mis en évidence par de nombreux auteurs en ce qui concerne les réactions en chaîne latérale.[8,9,31]

La vérification de la relation de Hammett exige que tous les termes de la série étudiée se transforment suivant un mécanisme identique (ex. S_N1 ou S_N2 limite). Lorsque ces dérivés subissent en chaîne latérale des réactions S_N2 caractérisées pour chaque terme par une valeur différente de la balance des facteurs "rupture" et "formation", l'équation de Hammett n'est par vérifiée, même d'une manière approchée et l'on obtient une courbe au lieu d'une droite.

L'existence d'une courbe, dans le mélange 79·5% dioxanne, n'a malheureusement pas pu être mise en évidence dans notre travail puisque nous ne disposons que de trois points.

L'effet d'un changement de mécanisme pourrait de même justifier les écarts observés au cours de substitutions nucléophiles ou électrophiles aromatiques[32] et attribuées, peut-être à tort, à l'importance des effets mésomères.

5. *Effet de la température sur la valeur de la constante de réaction*

Des graphiques de Hammett ont été tracés à 25°, 60° et 80° pour les dérivés *para* substitués dans les milieux 60·2% dioxanne, 39·8% dioxanne et 50·7% dioxanne (Tableau 17).

On obtient une relation linéaire à chaque température pour l'ensemble des milieux étudiés, y compris les milieux 39·8% dioxanne et 60·7% dioxanne pour lesquels les conditions relatives à la variation de log *PZ* ne sont pas vérifiées. Il doit nécessairement en être ainsi pour le milieu 50·7% dioxanne où l'énergie d'activation varie très peu d'un produit à l'autre mais les résultats obtenus pour le milieu 39·8% dioxanne sont incompatibles avec les théories de Hammett, Jaffe, Leffler et autres.

La relation $\rho T =$ constante se vérifie avec une bonne précision pour les dérivés *para* dans les milieux 79·5% et 60·2% dioxanne où log *PZ* est constant, et pour les dérivés *meta*- et non substitués dans le milieu 60·2% dioxanne où les valeurs extrêmes de log *PZ* diffèrent de 0·8.

Il n'en est pas de même pour les dérivés *meta* dans les milieux 39·8% dioxanne et 50·7% dioxanne où le facteur de fréquence varie très fort d'un substituant à l'autre. Les prévisions théoriques se vérifient donc exactement en ce qui concerne l'effet de la température sur la valeur de ρ.

[31] H. Kloosterziel et H. K. Backer, *J. Amer. Chem. Soc.* **74**, 5806 (1952).
[32] J. Miller, *Aust. J. Chem.* **9**, 61–73 (1956).

TABLEAU 17. APPLICATION DE LA RELATION DE HAMMETT AUX RÉACTIONS DE SOLVOLYSES DE CHLORURES D'α-PHÉNYLÉTHYLES SUBSTITUÉS

Etude de la constante de réaction ρ et du produit ρT

Dérivés	Milieu			25°		60°		80°	
	Eau	Dioxanne	Ac. form	ρ	ρT	ρ	ρT	ρ	ρT
p Cl-*p*CH_3-*p*F	20·5%	79·5%	—	−4·8	−1450	−4·5	−1510	−4·2	−1490
p Cl-*p*CH_3-*p*F	20·5%	79·5%	—	−5·3	—	—	—	—	—
	(corr.)								
p Cl-*p*CH_2-*p*F	5·8%	60·2%	34·0%	−5·5	−1650	−5·0	−1670	−4·7	−1670
m CH_3-H-*m* Cl	5·8%	60·2%	34·0%	−5·4	−1620	−4·9	−1660	−4·6	−1640
m CH_3-H-*m* Cl	6·1%	39·8%	54·1%	−5·8	−1730	−5·5	−1840	−5·4	−1920
m CH_3-H-*m* Cl	49·3%	50·7%	—	−5·3	−1570	−5·3	−1750	−5·2	−1850

TABLEAU 18. RELATION ENTRE LES ÉQUATIONS DE HAMMETT ET WINSTEIN–GRÜNWALD

O = dérivé de référence = dérivé non substitué
o = solvant de référence = 51·7% dioxanne–49·3% eau
X = dérivé étudié
x = solvant étudié

X	*x*			$\log k_{calc.}$	$\log k_{exp.}$
	Eau	Dioxanne	Ac. form.		
m Cl	66·6%	33·3%	—	−4·84	−5·01
	5·8%	60·2%	34·0%	−7·61	−7·50
	6·1%	39·8%	54·1%	−6·49	−6·52
	5·3%	25·8%	69·7%	−5·77	−5·90
m CH_3	20·5%	79·5%	—	−6·01	−6·00
	66·6%	33·3%	—	−5·28	−5·07
	5·8%	60·2%	34·0%	−4·16	−3·96
p Cl	66·6%	33·3%	—	−3·36	−3·44
	5·8%	60·2%	34·0%	−6·03	−6·00
	6·1%	39·8%	54·1%	−4·99	−4·98
	5·3%	25·8%	69·7%	−4·19	−4·28
p F	20·5%	79·5%	—	−5·80	−5·82
	66·6%	33·3%	—	−2·40	−2·32
	5·8%	60·2%	34·0%	−5·07	−5·14
	6·1%	39·8%	54·1%	−3·95	−4·03
	5·3%	25·8%	69·7%	−3·23	−3·31

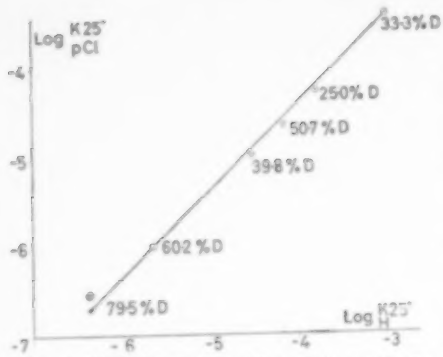

FIG. 1. Variation du logarithme de la constante de vitesse de solvolyse à 25° du chlorure d'α-(*p*-chlorophényl) éthyle dans différents milieux en fonction du logarithme de la constante de vitesse à la même température, du dérivé non substitué dans les mêmes milieux.

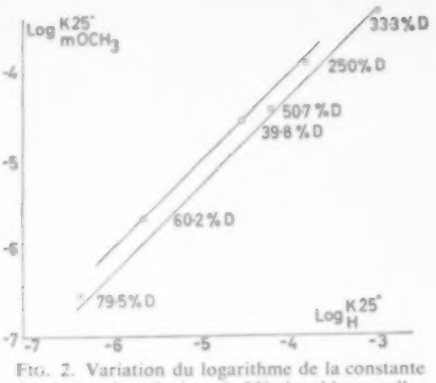

FIG. 2. Variation du logarithme de la constante de vitesse de solvolyse à 25° du chlorure d'α-(*m*-méthoxyphényl) éthyle dans différents milieux en fonction du logarithme de la constante de vitesse du dérivé non substitué dans les mêmes milieux.

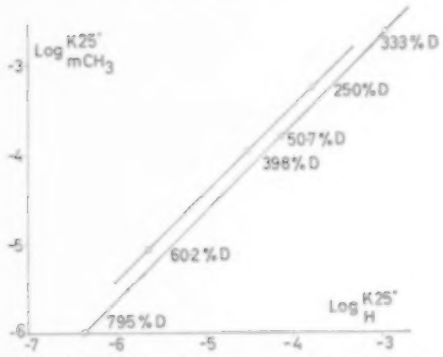

FIG. 3. Variation du logarithme de la constante de vitesse de solvolyse à 25° du chlorure d'α-(*m*-méthylphényl) éthyle dans différents milieux en fonction du logarithme de la constante de vitesse à la même température du dérivé non substitué dans les mêmes milieux.

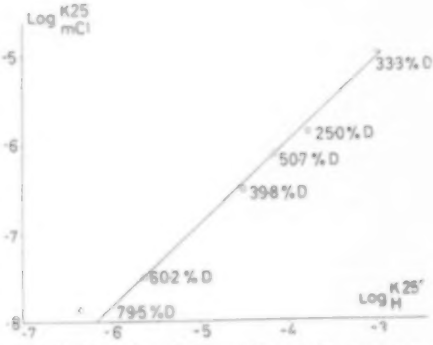

FIG. 4. Variation du logarithme de la constante de vitesse de solvolyse à 25° du chlorure d'α-(*m*-chlorophényl) éthyle dans différents milieux en fonction du logarithme de la constante de vitesse à la même température du dérivé non substitué dans les mêmes milieux.

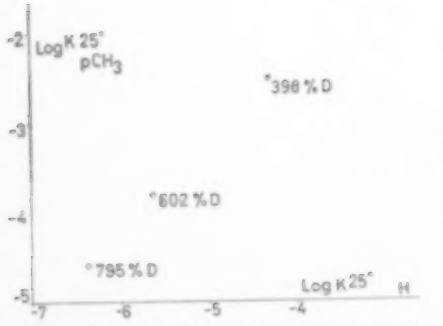

FIG. 5. Variation du logarithme de la constante de vitesse à 25° du chlorure d'α-(*p*-méthylphényl) éthyle dans trois milieux en fonction du logarithme de la constante de vitesse à la même température du dérivé non substitué dans les mêmes milieux.

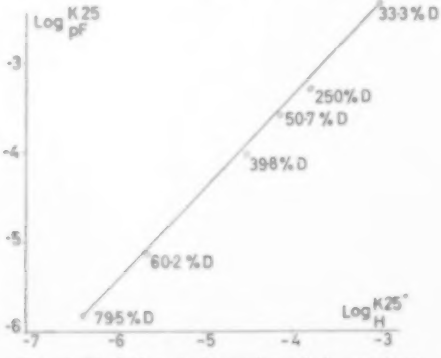

FIG. 6. Variation du logarithme de la constante de vitesse à 25° du chlorure d'α-(*p*-fluorophényl) éthyle dans différents milieux, en fonction du logarithme de la constante de vitesse à la même température, du dérivé non substitué dans les mêmes milieux.

VOL. 6 1959

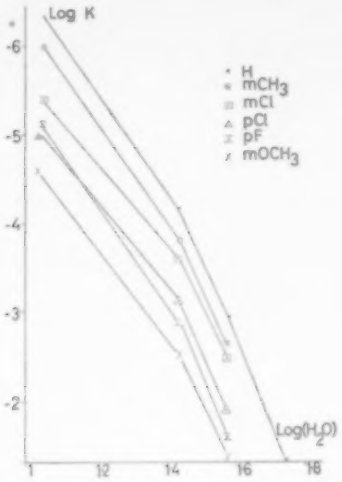

FIG. 7. Variation du logarithme de la constante de vitesse des dérivés en fonction de la teneur en eau des différents milieux.

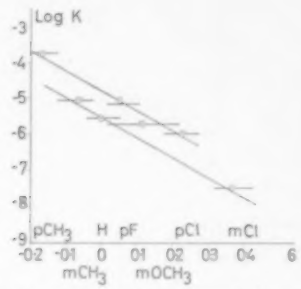

FIG. 8. Variation du logarithme de la constante de vitesse de solvolyse à 25° en fonction de la constante de substituant dans le milieu 60·2% dioxanne–34% acide formique–5·8% eau.

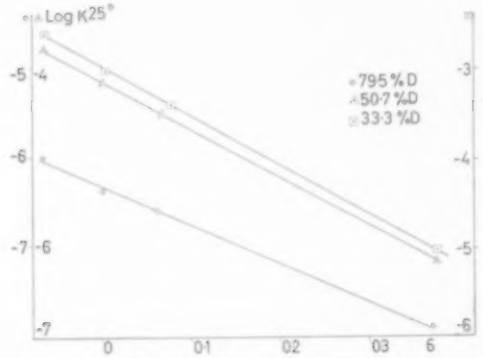

FIG. 9. Variation du logarithme de la constante de vitesse à 25° des dérivés *m*-CH_3, *m*-OCH_3, *m* Cl et non substitués en fonction de la constante de substituant dans les milieux binaires.

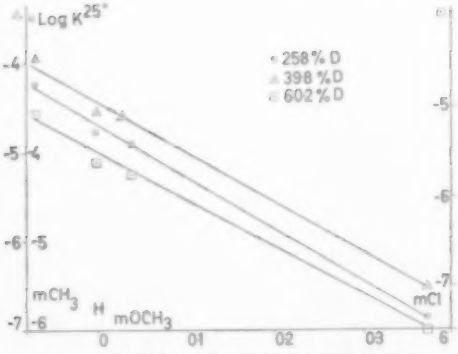

FIG. 10. Variation du logarithme de la constante de vitesse à 25° des dérivés *m*-CH_3, *m*-OCH_3, *m* Cl et non substitués en fonction de la constante de substituant dans les milieux ternaires.

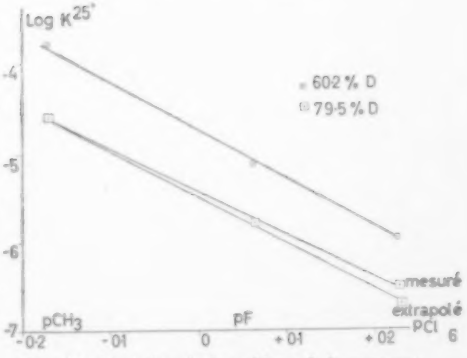

FIG. 11. Variation du logarithme de la constante de vitesse à 25° en fonction de la constante de substituant pour les dérivés *p*-CH_3, *p*-F et p-Cl substitués dans les milieux:
dioxanne 79·5%–eau 20·5%
dioxanne 60·2%–eau 5·8%–acide formique 34·0%

D. *Relation entre les équations de Hammett et Winstein–Grünwald*

Rappelons que lorsque le coefficient angulaire de la droite de Winstein–Grünwald est voisin de l'unité pour chacun des dérivés étudiés, cette relation s'énonce:

$$\log k_{Xx} = (\log k_{Xo} + \log k_{Oo}) + (\log k_{Ox} - \log k_{Oo}) + \log k_{Oo} \qquad (11)$$

où X = le dérivé étudié; x = le solvant étudié; O = le dérivé de référence; o = le solvant de référence.

Nous avons rassemblé dans le Tableau 18 les valeurs du logarithme de la constante de vitesse mesurées et calculées pour une série de dérivés réagissant par un mécanisme rigoureusement limite. L'accord entre la théorie et l'expérience est excellent; l'équation (22) est donc bien une relation générale entre les vitesses de solvolyse de différents produits dans différents milieux. L'utilité de cette équation est malheureusement très limitée puisqu'elle exige la vérification simultanée des équations de Hammett et de Winstein–Grünwald.

E. *Conclusions*

Nous avons montré que les résultats cinétiques relatifs à la solvolyse S_N1 d'une série de dérivés ne différant que par leur substituant, peuvent être interprétés à l'aide des équations de Hammett, Winstein–Grünwald et Tommila. La concordance parfaite entre les conclusions que l'on peut tirer de l'emploi de ces équations, même lorsqu'il s'agit de petits écarts, semble être une preuve du bien-fondé de l'interprétation que nous donnons.

Remerciements—Nous tenons à exprimer notre reconnaissance à Monsieur le Professeur R. H. Martin pour l'intérêt qu'il n'a cessé de porter à notre travail.

Nous remercions vivement le Laboratoire de Calcul Numérique de l'Université de Bruxelles qui a bien voulu se charger des calculs statistiques.

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DIE KONFIGURATION DER CARBONESTERGRUPPE UND DIE SONDEREIGENSCHAFTEN DER LACTONE*

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Zusammenfassung—Die Carbonestergruppe vermag in 2 Plankonfigurationen aufzutreten. Die Siedepunkte, Dipolmomente und RG-Konstanten der alkalischen Hydrolyse der homologen aliphatischen ω-Lactone (VII, $n = 4$ bis 16) lehren, dass die Ringstruktur bei VII, $n = 4$–7 die energiereiche *cis*-Konfiguration erzwingt, während VII, $n = 10$–16 wie offenkettige Ester *trans*-konfiguriert sind. VII, $n = 8, 9$ nehmen eine Übergangsstellung ein. Die leichte Lactonhydrolyse sowie die elektrophile Aktivität des ω-Kohlenstoffs sind charakteristisch für das *cis*-Carbonestersystem.

Abstract—The ester group exists in 2 planar configurations. The boiling points, dipole moments and rate constants of alkaline hydrolysis of the homologous aliphatic ω-lactones (VII, $n = 4$–16) show that the ring structure forces VII, $n = 4$–7 into the energetically rich *cis*-configuration; the members $n = 10$–16 assume the *trans*-configuration of the open-chain esters, while when $n = 8, 9$ an equilibrium is adopted. The easy lactone hydrolysis as well as the electrophilic activity of the ω-carbon atom are characteristic of the *cis*-ester structure.

SCHON FITTIG, der Entdecker der Lactone, machte auf deren ausgeprägte *Sondereigenschaften* im Rahmen der Carbonsäureester aufmerksam: In heissem Wasser stellt sich bereits das Hydrolysengleichgewicht der γ-Lactone mit γ-Hydroxysäuren ein;[1] δ-Lactone reagieren bereits in der Kälte.[2] Bei mässiger Wärme können aliphatische Lactone mit Natronlauge gegen Phenolphtalein unter Ringöffnung titriert werden. Diese Eigenschaften, an die man sich in den vergangenen 80 Jahren gewöhnt hat, erfuhren noch *keine befriedigende mechanistische Erklärung*. Im letzten Jahrzehnt fand die alkylierende Fähigkeit der β-Lactone[3] starke Beachtung; sie wurde meist auf die Baeyer-Spannung des 4-gliedrigen Ringes zurückgeführt. Dabei beachtete man nicht, dass auch γ-Lactone nucleophilen Substitutionen in der γ-Position, wenn auch erst unter energischeren Bedingungen, zugänglich sind.

Die Vermutung, dass eine von den offenkettigen Carbonestern abweichende *Konfiguration* der Estergruppe für die erhöhte Reaktivität der Lactone verantwortlich sei, erwies sich als zutreffend. Wir haben uns in den letzten Jahren mit der Konfiguration *drehungseingeschränkter* Bindungssysteme in mittleren Ringen[4] befasst. Das N-*monosubstituierte Carbonamid* beispielsweise tritt in zwei Plankonfigurationen (I und II) auf, deren wechselseitige Umwandlung des Aufwandes der Mesomerieenergie des Amidsystems bedarf. Das vergleichende Studium der physikalischen Eigenschaften 5-19-gliedriger *Lactame* (III)—die Konzentrationsabhängigkeit der Molpolarisation sowie die IR-Spektren waren besonders aufschlussreich—gestattete

* Mittlere Ringe, XV. Mitt.; XIV. Mitt.: R. Huisgen und U. Rietz, *Chem. Ber.* **90**, 2768 (1957).

[1] R. Fittig und W. H. Mielck, *Liebigs Ann.* **172**, 134 (1874); R. Fittig, *Ibid.* **200**, 62 (1880); **208**, 111 (1881); R. Fittig und M. B. Chanlaroff, *Ibid.* **226**, 333 (1884).

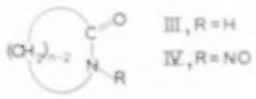
[2] R. Fittig und L. Wolff, *Liebigs Ann.* **216**, 127 (1883).

[3] Übersicht: H. E. Zaugg, *Org. Reactions* **8**, 305 (1954).

[4] Zusammenfassung: R. Huisgen, *Angew. Chem.* **69**, 341 (1957).

I II

den Rückschluss auf die Konfiguration.[5,6] In den Lactamen bis zum 9-gliedrigen Ring findet sich die durch den *ortho*Effekt benachteiligte *cis*-Konfiguration I erzwungen, während sich in den grösseren Lactamringen die Polymethylenkette über die *trans*-Positionen des Amidsystems (II) spannt.



III, R = H
IV, R = NO

Wesentlich drastischer wirkt sich der Konfigurationswechsel in der homologen Reihe der *Nitrosolactame* (IV) aus.[7] Das "Umklappen" der hier erheblich energiereicheren *cis*- in die *trans*-Konfiguration zwischen dem 9- und 10-gliedrigen Ring hat ein Absinken des Dipolmoments und der RG-Konstante der spontanen Acylwanderung zum cyclischen Diazoester zur Folge.

Wie im Carbonamid führt auch in der *Carbonestergruppe* die Mesomerie zur "Einebnung" des Bindungssystems. Die thermische Gleichgewichtseinstellung der beiden Konfigurationen V und VI, inbezug auf die drehungseingeschränkte CO-Bindung als *cis* und *trans* definiert, erscheint möglich, wenn man die Mesomerieenergie des Carbonestersystems im Bereich von 10–14 kcal vermutet. Die Dipolmomente der *offenkettigen* Carbonester weisen auf eine Bevorzugung der *trans*-Konfiguration VI.[8,9] Die Temperaturunabhängigkeit dieser Momente bietet eine Stütze für den *starren Bau* der Estergruppe.

Als erste Aufgabe ergibt sich somit die Prüfung der physikalischen Eigenschaften der homologen Reihe der aliphatischen ω-Lactone auf eventuelle *Sprungstellen*, die Rückschlüsse auf einen Konfigurationswechsel der eingebauten Estergruppe zulassen. Tritt ein solcher auf, dann gilt es, durch vergleichende Untersuchung der Reaktivität den Zusammenhang mit den Sondereigenschaften der Lactone herzustellen.

V VI

A. *Darstellung der ω-Lactone*

Zur Bereitung der grossgliedrigen ω-Lactone vom Nonanolid (VII, $n = 10$) aufwärts bewährte sich die Verdünnungscyclisierung der langkettigen ω-Brom-fettsäuren mit Kaliumcarbonat in

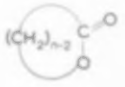
[5] R. Huisgen und H. Walz, *Chem. Ber.* **89**, 2616 (1956).
[6] R. Huisgen, H. Brade, H. Walz und I. Glogger, *Chem. Ber.* **90**, 1437 (1957).
[7] R. Huisgen und J. Reinertshofer, *Liebigs Ann.* **575**, 174, 197 (1952).
[8] A. Eucken und L. Meyer, *Physik. Z.* **30**, 397 (1929); C. T. Zahn, *Ibid.* **33**, 70 (1952); L. Meyer, *Z. physikal. Chem.* B **8**, 27 (1930); J. M. Sturtevant, *J. Amer. Chem. Soc.* **55**, 4478 (1933); C. T. Zahn, *Trans. Faraday Soc.* **30**, 804 (1934).
[9] R. J. B. Marsden und L. E. Sutton, *J. Chem. Soc.* 1383 (1936).

Methyläthylketon nach Hunsdiecker und Erlbach.[10] Die Lactone gewöhnlicher Ringgrösse sind bequem zugänglich, das ε-Caprolacton (Hexanolid, VII, $n = 7$) z.B. durch Ringerweiterung des *Cyclo*hexanons mit Perbenzoesäure.[11]

Bei VII, $n = 8, 9$ klafft eine Lücke in der Reihe der bekannten Lactone. Die innermolekulare Veresterung der ω-Hydroxycarbonsäuren mit Benzolsulfonsäure in Benzol[12] versagt hier ebenso wie die obenerwähnte intramolekulare Alkylierung der ω-Brom-fettsäuren.[10] Die Depolymerisation der Polyester unter dem Einfluss elektrophiler Katalysatoren[13] liefert hier ausschliesslich dimere Lactone mit 16- und 18-gliedrigem Ring. Die Reaktion des *Cyclo*heptanons und -octanons mit Perbenzoesäure verläuft ungemein langsam und gibt anstelle der empfindlichen VII, $n = 8, 9$ nur die Polyester.[11]

Angesichts des bekannten Minimums in der *Bildungstendenz* mittlerer Ringe erschien uns die Umsetzung der Ringketone mit Persäuren aussichtsreicher als eine Ringsynthese. Es galt, eine Persäure zu finden, die rascher reagiert als Perbenzoesäure, um die bei langen Reaktionszeiten unvermeidliche Polyesterbildung einzuschränken. Nach mechanistischen Studien[14] enthält die Umsetzung mit Ketonen ein säurekatalysiertes Additionsgleichgewicht mit anschliessender, zum Carboxylatanion führender *Heterolyse der Peroxydbindung*. Mit der Erwartung, dass die Geschwindigkeit der Heterolyse der Persäure und ihrer Abkömmlinge mit der *Acidität* der zugrundeliegenden Carbonsäure wächst, stimmen die Criegee-Umlagerung der Dekalyl-perester[15] sowie die Epoxydation der Alkene mit aromatischen Persäuren[16] überein.

Tatsächlich vollzog sich die Umsetzung des *Cyclo*heptanons und -octanons mit *Pertrifluoressigsäure* in Methylenchlorid in Gegenwart von Dinatriumphosphat—das sind die Bedingungen von Emmons und Lucas[17]—glatt und ergab 68% VII, $n = 8$ resp. 72% VII, $n = 9$.[18] Als Nebenprodukt lieferte *Cyclo*heptanon noch das dimere Peroxyd VIII.



VII

VIII

Die Konstitution dieser letzten, bislang fehlenden Glieder der ω-Lactonreihe wurde neben Analyse und Äquivalenttitration durch die *Hydrazinolyse* gesichert, die nahezu quantitativ ω-Hydroxy-önanthsäure- bzw. -caprylsäure-hydrazid lieferte.

[10] H. Hunsdiecker und E. Erlbach, *Chem. Ber.* **80**, 129 (1947).
[11] S. L. Friess, *J. Amer. Chem. Soc*, **71**, 2571 (1949); S. L. Friess und P. E. Frankenburg, *Ibid.* **74**, 2679 (1952); vgl. R. Robinson und L. H. Smith, *J. Chem. Soc.* 371 (1957).
[12] M. Stoll und A. Rouve, *Helv. Chim. Acta* **18**, 1087 (1935). Die Ringbildungsgeschwindigkeit zeigte bei VII, $n = 8, 9$ ein Minimum. Bei einem geringen Vorlauf des Produktes aus ω-Hydroxy-önanthsäure wurde aus dem Geruch auf VII, $n = 8$ geschlossen. VII, $n = 9$, angeblich zu 0·98% entstanden, konnte ebenfalls nicht analysenrein erhalten werden.
[13] E. W. Spanagel und W. H. Carothers, *J. Amer. Chem. Soc.* **57**, 929 (1935); **58**, 654 (1936).
[14] W. v. E. Doering und L. Speers, *J. Amer. Chem. Soc.* **72**, 5515 (1950); S. L. Friess und A. H. Soloway, *Ibid.* **73**, 3968 (1951); W. v. E. Doering und E. Dorfman, *Ibid.* **75**, 5595 (1953).
[15] R. Criegee, *Liebigs Ann.* **560**, 127 (1948); P. D. Bartlett und J. L. Kice, *J. Amer. Chem. Soc.* **75**, 5591 (1953).
[16] S. Medwedew und O. Bloch, *Chem. J. Ser. W. J. physikal. Chem.* **4**, 721 (1933); *Chem. Zentralbl.* **I**, 2670 (1935).
[17] W. D. Emmons und G. B. Lucas, *J. Amer. Chem. Soc.* **77**, 2287 (1955).
[18] R. Huisgen und H. Ott, *Angew. Chem.* **70**, 312 (1958).

Nur das Heptanolid (VII, $n = 8$) teilt mit dem ε-Caprolacton (VII, $n = 7$) die ausgeprägte Polymerisationsbereitschaft.

B. *Dipolmomente und Siedepunkte*

Zu Beginn unserer Arbeit fanden sich nur die elektrischen Momente des β-Propio-[19] and des γ-Butyrolactons[9] beschrieben. Wir haben die Dipolmomente der homologen Reihe VII, $n = 5$–16 in Benzol bei 25° aus den Parametern der Tab. 1 mittels des Näherungsverfahrens von Hedestrand[20] bestimmt. Die Funktionen

TABELLE 1. DIPOLMOMENTE DER HOMOLOGEN REIHE DER ω-LACTONE IN BENZOL BEI 25°

$\Delta\varepsilon/\gamma_2$ = Steigung der Dielektrizitätskonstanten-Molenbruch-Funktion; $\Delta d/\gamma_2$ = Steigung der Dichte-Molenbruch-Funktion; $P_{2\infty}$ = Molpolarisation bei unendl. Verdünnung; R_D = Molrefraktion bei der D-Linie, aus Inkrementen berechnet.

Lacton VII, n =	Sdp. bei 10–11 Torr	$\Delta\varepsilon/\gamma_2$	$\Delta d/\gamma_2$	$P_{2\infty}$	R_D	μ (in D)
4[19]	51°					3·8[19]
5	79–80°	23·19	0·258	342	20·0	4·09
6	97–98°	24·64	0·258	388	24·7	4·22
7	104–106°	25·49	0·268	405	29·4	4·45
8	80–82°	18·96	0·281	314	34·0	3·70
9	72–73°	6·92	0·264	142	38·7	2·25
10	86–87°	5·50	0·258	126	43·4	2·01
11	100°	4·79	0·258	120	48·0	1·88
12	116°	4·64	0·242	124	52·7	1·86
13	130°	4·62	0·237	128	57·3	1·86
14	143°	4·59	0·234	133	62·0	1·86
16	169°	4·54	0·224	142	71·3	1·86
Capronsäure-*n*-butylester	83°	3·75	−0·055	115	50·1	1·79

$\Delta\varepsilon/\gamma_2$, bis zu Molenbrüchen der Lactone $\gamma_2 = 0{\cdot}015$ gemessen, erwiesen sich als streng linear; man hat somit in diesem Konzentrationsbereich nicht mit einer *Assoziation* zu rechnen.[21] Beiläufig sei erwähnt, dass die Funktion $\Delta d/\gamma_2$, die den Dichtezuwachs der Lösung in Abhängigkeit vom Molenbruch des Lactons wiedergibt, bei VII, $n = 8$ ein *Maximum* passiert;[22] bei den Lactamen III lag dieses Maximum bei $n = 10$.[5]

Bezüglich der Dipolmomente lassen die ω-Lactone 2 Gruppen erkennen: VII, $n = 4$–8 mit Momenten von 3·7–4·4 D und VII, $n = 9$–16 mit solchen von 2·2–1·9 D

[19] T. L. Gresham, J. E. Jansen und F. W. Shaver, *J. Amer. Chem. Soc.* **70**, 998 (1948).

[20] G. Hedestrand, *Z. Physik. Chem.* B **2**, 428 (1929); vgl. auch J. W. Smith, *Electric Dipole Moments* Butterworths, London (1955); R. J. W. LeFevre, *Dipole Moments* 3. Aufl. Methuen London (1953); J. Czekalla, *Z. Elektrochem. Angew. Physik Chem.* **60**, 145 (1956).

[21] Obwohl die *Lactame* III kleinere Dipolmomente haben als VII, 5–7, zeigen die Lactame eine *starke Assoziation*.[5] Wir vermögen daher der Argumentation von C. G. Cannon, *Mikrochim. Acta* 555, (1955), nicht zu folgen, der die Amidassoziation auf Dipolwechselwirkung zurückführt. Die *Wasserstoffbrücke* scheint uns auch die einzige Erklärungsmöglichkeit für die *unterschiedlichen Assoziationsformen* der *cis*- und *trans*-Lactame zu bieten.[5]

[22] Dagegen nehmen die Dichten der reinen Lactone mit der Ringgrösse stetig ab. Stoll und Rouve[12] schliessen aus dem Vergleich mit den Dichtekurven der Di- und Trilactone auf die Kompression im mittleren Ringgebiet; M. Stoll und G. Stoll-comte, *Helv. Chim. Acta* **13**, 1185 (1930).

(Tabelle 1). Dabei nehmen die 8–10-gliedrigen Lactone eine gewisse Übergangsstellung ein. Mit 1·86*D* zeigen VII, $n = 12$–16 ein konstantes Dipolmoment; Länge und Faltung der Polymethylenkette sind hier also praktisch ohne Einfluss.

Die *grossgliedrigen* Lactone stimmen mit den *offenkettigen* Estern in der Grössenordnung des Dipolmoments überein, wie das Beispiel des Capronsäure-*n*-butylesters dartut.[23] Eine naheliegende Arbeitshypothese weist den Lactonen VII, $n = 4$–8

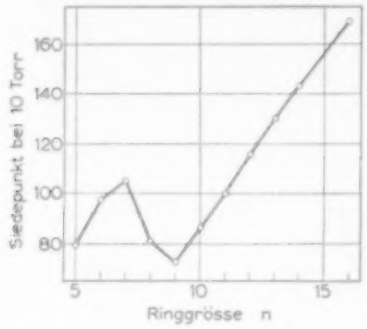


FIG. 1. Siedepunkte der homologen ω-Lactone.

die durch den Ringschluss erzwungene *cis*-Esterkonfiguration V zu, während die grossgliedrigen Lactone wie die offenkettigen Carbonester über die *trans*-Konfiguration VI verfügen. Den letzten Schluss zogen bereits Marsden und Sutton[9] in einer schönen Arbeit aus dem zu 4·12*D* gefundenen Moment des Butyrolactons.[24] Der niedrigere Energiegehalt der *trans*-Estergruppe, der bevorzugten Konfiguration, findet eben im kleineren elektrischen Moment eine anschauliche Illustration.

Die Dipolassoziation beeinflusst die *Verdampfungswärme* der Lactone erheblich. Wie Fig. 1 zeigt, sieden die *cis*-Lactone um etwa 130° höher als die *trans*-Lactone, wenn man deren Siedepunktsintervalle bei CH_2-Zuwachs zugrundelegt.

Es entspricht der Erwartung, dass *cis*-Ester über ein *höheres* Dipolmoment verfügen als *trans*-konfigurierte. Es ist nun verlockend, die *Zerlegung in Partialmomente* durchzuführen, um den Einfluss der Estermesomerie zahlenmässig zu erfassen. Die Summenmomente von *cis*- und *trans*-Ester gestatten es dabei, die Grösse zweier Partialmomente anzugeben, wenn der von ihnen eingeschlossene Winkel als bekannt angenommen wird. Für die Geometrie des Carbonestersystems in Lösung dürften die Bindungswinkel und -abstände offenkettiger Ester im Gaszustand die beste Näherung bieten; die Daten der Fig. 2 gründen sich auf Elektronenbeugungsaufnahmen von O'Gorman *et al.*[25]

Der Zerlegung liegen folgende Vereinfachungen zugrunde:

1. Die Bindungswinkel und -abstände des offenkettigen Esters werden nicht

[23] In guter Übereinstimmung fanden K. L. Wolf und W. J. Gross, *Z. phys. Chem.* B **14**, 305 (1931) die elektrischen Momente des Propionsäure-*n*-propyl- und -*n*-butylesters in Benzol bei 22° zu 1·76 bzw. 1·77*D*.

[24] In E. A. Braude und F. C. Nachod, *Determination of Organic Structures by Physical Methods* S. 405. Academic Press, New York (1955), erwähnt L. E. Sutton unveröffentl. Dipolmomente einiger weiterer Lactone (VII): 4·20 für $n = 6$, 4·33 für $n = 7$, 2·1 für $n = 10$; 1·90 für $n = 16$. Wir wurden auf diese Daten erst nach Abschluss unserer Messungen aufmerksam. Suttons Werte—Lösungsmittel, Temperatur und Berechnungsverfahren wurden nicht angegeben—stehen mit unseren befriedigend in Einklang.

[25] J. M. O'Gorman, W. Shand und V. Schomaker, *J. Amer. Chem. Soc.* **72**, 4222 (1950).

nur für die *trans*-, sondern auch für die *cis*-Lactone übernommen; im letzteren wird also die untere Molekülhälfte der Fig. 2 gespiegelt;

2. Das gesamte Bindungssystem gemäss Fig. 2 wird als *eben* betrachtet; der 20–25° betragende Winkel der C—O—C″-Ebene gegen die O=C—O-Ebene[25] wird vernachlässigt;

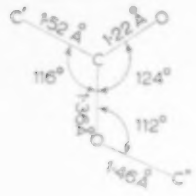


FIG. 2.

FIG. 3.

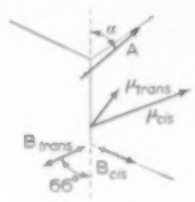


FIG. 4

3. Der Vorzug der *trans*-Konfiguration ist so gross, dass die geringe Gleichgewichtskonzentration der *cis*-Form das elektrische Moment der grossgliedrigen Lactone und der offenkettigen Ester praktisch nicht beeinflusst (S. 262);

4. Die Normwerte der Dipolmomente von *cis*- und *trans*-Lacton werden zu 4·30 und zu 1·86 *D* angenommen, was hinsichtlich der ersteren eine gewisse Willkür einschliesst.

Die 5 Partialmomente der Fig. 3 werden zu den Vektoren *A* and *B* der Fig. 4 addiert. Am "Äthermoment" *B* sind neben den Bindungsmomenten *c* und *d* das von den Orbitals der einsamen Elektronenpaare herrührende Moment[26] *e* beteiligt. Die von der Estermesomerie ausgelöste Verkürzung des C—O-Abstandes sowie die sp^2-Hybridisierung des Carbonylkohlenstoffs verkleinern *c* gegenüber *d*. Dem kaum exakt angebbaren Unterschied wird mit einer 10°-Abweichung des Äthermoments *B* von dem Vektor *e* Rechnung getragen. Das Carbonylmoment *a* und das "Mesomerie-Moment" *b*, der Beteiligung der dipolaren Grenzformel entspringend, ergeben das "Ketonmoment" *A*. Der Winkel α, den *A* mit der C—O-Achse einschliesst, hängt vom Grössenverhältnis *a* : *b* ab. In Tabelle 2 finden sich die für verschiedene Verhältnisse *a* : *b* berechneten Partialmomente aufgeführt.

Das *Partialmoment A* ist um etwa 0·6 *D* grösser als das Dipolmoment aliphatischer Ketone mit 2·74 ± 0·05 *D*.[27] Unter der vereinfachenden Annahme, dass das Carbonylmoment *a* der Lactone mit dem der Ketone übereinstimmt, ergibt sich ein Wert von 1 : 4·2 für das Grössenverhältnis *a* : *b* (Tabelle 2; die Vektoren der Fig. 4 beziehen sich auf $a/b = 4$). Ein Vektor des "mesomeren" Moments *b* von 0·65 *D* würde auf eine *6-proz. Beteiligung* der zwitterionischen Grenzformel am Grundzustand des Carbonestersystems schliessen lassen. Abgesehen davon, dass die Vereinfachungen sich in einer Verminderung dieses Prozentsatzes auswirken, sei darauf hingewiesen, dass Dipoldaten stets *niedrigere* Werte für die mesomere Beteiligung zwitterionischer Grenzformeln ergeben haben als andere Moleküldaten.[28]

[26] J. Lennard-Jones und J. A. Pople, *Proc. Roy. Soc.* A **202**, 166 (1950); J. A. Pople, *Ibid.* **202**, 323 (1950).

[27] Nach H. H. Günthard und T. Gäumann, *Helv. Chim. Acta* **34**, 39 (1951) liegen die Dipolmomente der Cyclanone bis zum 9 gliedrigen Ring aus unbekannten Gründen höher, während diejenigen der grossgliedrigen Ringketone dem obigen Normalwert der offenkettigen Ketone entsprechen.

[28] C. P. Smyth, *Dielectric Behavior and Structure* S. 254. McGraw-Hill, New York (1955). Folgt man dem Vorschlag von J. A. C. Hugill, I. E. Coop und L. E. Sutton, *Trans. Faraday Soc.* **34**, 1518 (1938), und berücksichtigt die *Momentminderung durch Induktion* mit einem Faktor von 0·6, dann gelangt man zu einer 10-*proz. Beteiligung* der zwitterionischen Struktur. Marsden und Sutton[9] schätzten den Anteil auf der Grundlage der damals bekannten Daten zu 8%.

TABELLE 2. ERMITTLUNG DER PARTIALMOMENTE DER CARBONESTERGRUPPE IN LACTONEN GEMÄSS FIG. 3, 4

$a:b$	α	A	B	a	b
1	41°	3·36*D*	1·82*D*	1·74*D*	1·74*D*
2	46	3·35	1·70	2·30	1·15
3	49	3·33	1·62	2·57	0·86
4	50	3·32	1·57	2·71	0·68
5	51	3·31	1·54	2·82	0·56

VOL. 6 1959

Das *Äthermoment B* ist mit 1·6–1·8*D* zwar wesentlich grösser als das der Dialkyläther (1·2*D*), liegt aber mit denen des Tetrahydrofurans (1·70*D*) und Tetrahydropyrans (1·9*D*) in gleicher Grössenordnung. Solange die erhebliche Differenz der Dipolmomente offenkettiger und cyclischer Äther nicht befriedigend geklärt ist[29] und die Momente grösserer Polymethylenoxydringe unbekannt sind, ist ein Rückschluss auf die Elektronegativität des Äthersauerstoffs im Estersystem nicht möglich.

Die Dipolmomente der *cis*-Lactone VII, $n = 4$–7 steigen mit zunehmender Ringgrösse (Tabelle 1). Es liegt nahe, für die geringeren Momente der 4- und 5-gliedrigen Lactone die *Dämpfung der Carbonester-Mesomerie*, durch die Winkelabweichung erzwungen, verantwortlich zu machen. In gleicher Richtung weisen die infraroten Carbonyl-Schwingungsfrequenzen der Lactone mit $4 > 5 > 6$ sowie die mit der Ringgrösse zunehmende Befähigung, als Acceptor für H-Brücken zu dienen.[30] Der Unterschied der Dipolmomente von VII, $n = 6$ und 7 ist ungeklärt.

Das elektrische Moment der *trans*-Carbonestergruppe schliesst mit der C′—C-Bindungsachse der Fig. 2 einen Winkel von 80°, das der *cis*-Estergruppe einen solchen von 46° ein (Fig. 4). Für das Moment der Carboxylgruppe, ebenfalls der *trans*-Konfiguration entsprechend, wurde aus Messungen an subst. Benzoesäuren empirisch ein Winkel von 74° ermittelt.[31]

C. *Die Kinetik der alkalischen Lacton-Hydrolyse*

Die früheren Arbeiten beschäftigten sich vornehmlich mit γ-Lactonen;[32] H. Sebelius[33] bezog auch δ-Lactone ein und fand die RG-Konstante des δ-Valerolactons 20 mal grösser als die des γ-Butyrolactons. Dieser Reaktivitätsunterschied diente in der Zuckerchemie zur Unterscheidung furanoider und pyranoider Onsäure-lactone.[34] Eine systematische Untersuchung des Einflusses der Ringgrösse auf die Hydrolysengeschwindigkeit der Lactone fehlt bislang, was angesichts der S. 253 erwähnten Sonderstellung der inneren Ester geradezu überrascht.

Die Methodik der kinetischen verfolgung der vieluntersuchten, alkalischen Esterhydrolyse ist einfach; lediglich die *Wahl des Lösungsmittels* verursachte im Hinblick auf die hohen RG-Konstanten

[29] C. P. Smyth, *Dielectric Behavior and Structure* S. 297.[36]
[30] S. Searles, M. Tamres und G. M. Barrow, *J. Amer. Chem. Soc.* **75**, 71 (1953).
[31] C. S. Brooks und M. E. Hobbs, *J. Amer. Chem. Soc.* **62**, 2851 (1940); M. E. Hobbs und A. J. Weith, *Ibid.* **65**, 967 (1943).
[32] P. Henry, *Z. Physik. Chem.* **10**, 96 (1892); S. S. G. Sircar, *J. Chem. Soc.* 898 (1928). D. S. Hegan und J. H. Wolfenden, *Ibid.* 508 (1939).
[33] Dissertation Lund 1927; die Daten finden sich bei W. Hückel, *Theoretische Grundlagen der Organischen Chemie* 8. Aufl. Bd. II, S. 762. Akad. Verlagsges. Leipzig (1957).
[34] H. S. Isbell und C. S. Hudson, *J. Res. Nat. Bur. Stand.* **8**, 327 (1932).

Schwierigkeiten. In Vorversuchen zeigte 75-vol. proz. *Methoxy-äthanol* ausreichendes Lösungsvermögen. Während sich die Hydrolyse des γ-Butyrolactons in diesem Lösungsmittel ohne Störung messen liess, trat bei ε-Caprolacton eine Komplikation auf: Nach sehr raschem Anfangsverbrauch von HO^- vollzog sich die Verseifung recht langsam; Zweifel an der Reinheit des ε-Lactons erwiesen sich als unbegründet. Es stellte sich heraus, dass innerhalb Minutenfrist bei 0° die alkalikatalysierte *Umesterung* zum ε-Hydroxy-capronsäure-methoxyäthylester abgeschlossen war und der weitere HO^--Verbrauch der viel langsameren Hydrolyse dieses offenkettigen Esters entsprach. Dass bei VII, $n = 5$ die Umesterung nicht mit der Hydrolyse zu konkurrieren vermochte, beleuchtet einen interessanten und noch ungeklärten Unterschied.

Die in *60-proz. Dioxan* ermittelten RG-Konstanten der alkalischen. Hydrolyse finden sich in Tabelle 3 incl. der Arrhenius–Parameter zusammengestellt. Die Hydrolyse von VII, $n = 5$–8 war schon bei 0° so rasch, dass wir auf die Messung der Temperaturabhängigkeit verzichteten; da schon bei −3° Dioxan aus dem Solvens zu kristallisieren begann, verboten sich Messungen bei tieferen Temperaturen. Zum Vergleich wurden daher alle RG-Konstanten auf 0° extrapoliert (Tabelle 3). Die *erste Reaktionsordnung* bezügl. des Lactons liess sich leicht durch Messungen mit unterschiedlichen Anfangskonzentrationen dartun. Auch für das Hydroxylion unterliegt sie keinem Zweifel, wenngleich hier der erhebliche Ionenstärken-Effekt der Konzentrations-variation engere Grenzen setzte.

Die auf 0° bezogenen RG-Konstanten erstreckten sich über *5 Zehnerpotenzen* und bilden, wie leicht erkennbar, 2 Gruppen: Die Lactone VII, $n = 5$–8 zeigen viel höhere spezif. Reaktionsgeschwindigkeiten als VII, $n = 10$–16; Octanolid (VII, $n = 9$) liegt dazwischen. Die RG-Konstanten und Aktivierungsparameter der grossen Lactonringe entsprechen denen offenkettiger Carbonester, wie das Beispiel des Capronsäure-butylesters lehrt. Der Schluss, dass die beiden Gruppen, die sich in den k_2-Werten um 3–4 Zehnerpotenzen unterscheiden, den Lactonen mit *cis*- und *trans*-konfiguriertem Carbonestersystem entsprechen, erscheint nicht sehr gewagt.

Die grössere Reaktivität der *cis*-Lactone ist recht einfach zu interpretieren. Nach wohlbegründeten theoretischen Vorstellungen vollzieht sich die alkalische Carbonesterhydrolyse über ein HO^--Addukt als Zwischenstufe;[35] die Bildung dieses Addukts ist

RG-bestimmend. Bei der Anlagerung des Hydroxylions entsteht aus dem *trigonalen* Carbonylkohlenstoff ein *tetraedrisches* Zentrum. Beim Übergang in IX geht nicht nur die Estermesomerie verloren; auch der konfigurative Unterschied von *cis*- und *trans*-Ester wird nahezu gegenstandslos. Zwar verhindert der Lactonring in der IX entsprechenden Zwischenstufe die freie Rotation, die der R'O—C-Bindung in IX zukommt. Die Inspektion des Modells lässt für die aus *cis*- und *trans*-Lactonen hervorgehenden Hydroxyl-addukte *keinen wesentlichen Energieunterschied* mehr erwarten. Wenn man das gleiche bereits für die Übergangszustände (*T* in Fig. 5) postuliert, die vermutlich den Zwischenstufen schon strukturell nahestehen, dann geht die grössere Reaktionsgeschwindigkeit der *cis*-Lactone auf deren *höheres Energieniveau im Grundzustand* zurück (Fig. 5).

[35] M. L. Bender, *J. Amer. Chem. Soc.* **73**, 1626 (1951).

TABELLE 3. KINETIK DER HYDROLYSE DER ω-LACTONE MIT NaOH IN DIOXAN-WASSER (60 : 40 Vol%).

Lacton VII n =	T (°C)	$10^4 \cdot k_2$ (l/Sek . Mol)	$E_A(\pm 0{\cdot}2)$ in kcal	log A	$10^4 k_2$ bei 0° (l/Sek . Mol)
5	+0·10	1 480			1 480
6	0·10	55 000			55 000
7	0·10	2 550			2 550
	0·20	2 620			
8	0·10	3 530			3 530
9	0·10	117	11·7	7·43	116
	10·82	261			
	20·40	519			
10	60·28	35·2	15·2	7·50	0·22
	66·92	55·5			
	74·68	91·1			
11	60·16	53·1	13·7	6·72	0·55
	67·18	81·3			
	74·76	126·5			
12	50·88	97	11·7	5·89	3·3
	60·02	159			
	69·46	260			
13	50·26	130	10·7	5·35	6·0
	60·16	211			
	69·08	323			
14	60·20	145	11·7	5·84	3·0
	67·10	208			
	75·54	315			
16	60·18	240	10·8	5·47	6·5
	66·82	330			
	74·22	465			
Capronsäure-*n*-butylester	52·32	227	11·1	5·82	8·4
	59·88	336			
	67·66	493			

Man kann zu einer Abschätzung des *Energieunterschieds* zwischen *cis*- und *trans*-Carbonester gelangen. Wenn man die RG-Konstanten von VII, $n = 7$ und 14 als typisch für *cis*- bzw. *trans*-Ester betrachtet, dann gilt:

$$\Delta\Delta F = -RT \ln (k_{cis}/k_{trans}) = 3{\cdot}8 \text{ kcal}$$

Diesen Unterschied der *freien Aktivierungsenergie* darf man mit der *Differenz* der potentiellen Energie von *cis*- und *trans*-Lacton in Beziehung setzen, wenn man in grober Näherung die potentiellen Energien der Übergangszustände gleichsetzt und mit den Aktivierungsentropien ebenso verfährt. Mit einem Energieunterschied in dieser Grössenordnung hätte man für *trans*-Ester bei Raumtemp. nur mit einer Gleichgewichtskonzentration von 0·15% *cis*-Ester zu rechnen.

Eine so kleine Gleichgewichtskonzentration an *cis*-Carbonester ist in den normalen *trans*-Estern mit den zur Verfügung stehenden physikalischen Methoden nicht mehr nachweisbar. Es erscheint

jedoch möglich, dass die alkalische Hydrolyse der *trans*-Carbonester, zumindest teilweise, über die bescheidene Konzentration an der *cis*-Konfiguration erfolgt. Experimente, die diesen Anteil abzuschätzen gestatten, liegen noch nicht vor.

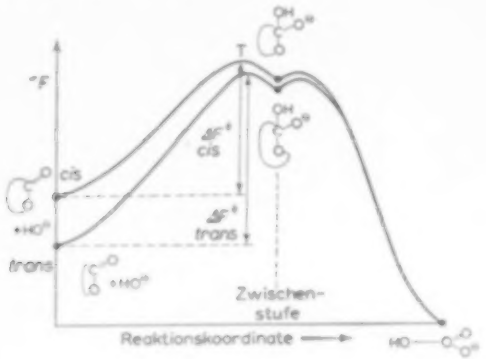


FIG. 5. Energieprofile der alkalischen Hydrolyse von *cis*- and *trans*-Lactonen.

Auch die im Vergleich mit dem γ-Lacton (VII, $n = 5$) um einen Faktor 40 grössere RG-Konstante des δ-Lactons (VII, $n = 6$) ist plausibel. Während sich die Carbonylgruppe des 5-gliedrigen Ringes gegen die Erhöhung der Koordinationszahl, die mit der Hydroxyl-Anlagerung verbunden ist, aus *konformativen* Gründen sträubt, ist diese Umsetzung beim 6-gliedrigen Ring mit einem Nachlassen der *Pitzer-Spannung* verbunden.[36] Nicht minder charakteristisch ist das Passieren eines Minimums der RG-Konstanten bei VII, $n = 10, 11$ (Tabelle 3). In diesen zweifellos *trans*-konfigurierten Lactonen erreichen *konformative Spannung* und *Pressung der van der Waals-Radien* das für *mittlere Ringe* bekannte Maximum.[37] Diese Faktoren wirken der für die Hydrolyse erforderlichen Überführung eines trigonalen in ein tetraedrisches Ringglied entgegen und haben einen beachtlichen Anstieg der Aktivierungsenergie zur Folge. Schon in VII, $n = 13$ scheint dieser "mittlere Ring-Effekt" erloschen zu sein.

Die leichte Hydrolysierbarkeit als Sondereigenschaft der Lactone (S. 253/4) wurde somit als Charakteristikum des *cis*-Carbonestersystems erkannt. Auch die insbesondere an γ-Lactonen studierte Fähigkeit zur *Alkylierung nucleophiler Agentien*, die den strukturell entsprechenden offenkettigen Estern fehlt, wird durch das *höhere Energieniveau* der *cis*-Estergruppe ermöglicht:

Die Reaktionen mit Cyanid,[38] anionischen Sauerstoff- und Schwefelfunktionen[39] sowie Aminen,[40] vor allem von Reppe studiert, sind hier anzuführen. Auch die

[36] H. C. Brown, J. H. Brewster und H. Shechter, *J. Amer. Chem. Soc.* **76**, 467 (1954).
[37] V. Prelog, *J. Chem. Soc.* 420 (1950); R. Huisgen, *Angew. Chem.* **69**, 341 (1957).
[38] W. Wislicenus, *Liebigs Ann.* **233**, 101 (1886); G. Blanc, *Bull. Soc. Chim. Fr.* [3] **33**, 879 (1905).
[39] R. Fittig und K. T. Ström, *Liebigs Ann.* **267**, 186 (1892); H. Plieninger, *Chem. Ber.* **83**, 265 (1950); L. Schotte, *Arkiv f. Kemi* **8**, 457 (1955).
[40] W. Reppe, *Liebigs Ann.* **596**, 158 (1955).

Bereitschaft der γ-Lactone zur Friedel–Crafts-Alkylierung von Aromaten[41] spricht für die leichte Heterolyse der C—O-Bindung in *cis*-Estern; nach eigenen Versuchen geht dem Exaltolid (VII, $n = 16$) diese Fähigkeit ab. In den β-Lactonen werden die Ringöffnungen noch zusätzlich durch die Lösung der *Baeyer–Spannung* begünstigt.

Auch in der starken *Polymerisationsbereitschaft* scheint ein Monopol der *cis*-Lactone mit Ausnahme derjenigen mit 5-gliedrigem Ring vorzuliegen. Für VII, $n = 4$, 6 und 7 fand sich diese Eigenschaft bereits beschrieben;[42] das hier erstmalig

TABELLE 4. EIGENSCHAFTEN DER ALIPHATISCHEN ω-LACTONE IM BEREICH DES KONFIGURATIONSWECHSELS

VII, n =	Sdp. bei 10–11 Torr	Dipolmoment μ	$10^4 k_2$ bei 0° (alkalische) Hydrolyse	Esterkonfiguration
7	104–106°	4·45	2 550	*cis*
8	80–82°	3·70	3 530	*cis* + wenig *trans*
9	72–73°	2·25	115	*trans* + wenig *cis*
10	86–87°	2·01	0·22	*trans*

dargestellte VII, $n = 8$ schliesst sich dem ε-Caprolacton eng an. Man darf vermuten, dass diese noch wenig untersuchten thermischen Polyesterbildungen—möglicherweise handelt es sich doch um katalytische Prozesse—mit einer Carbonyladdition einsetzen.

D. *Zum Konfigurationswechsel der Lactone im mittleren Ringgebiet*

Zur Festlegung der Stelle des Wechsels der Esterkonfiguration in der homologen Lactonreihe seien in Tab. 4 die Eigenschaften der Glieder des Übergangsbereiches verglichen. Schon die Siedepunktskurve (Fig. 1) kennzeichnet das *Heptanolid* (*VII*, $n = 8$) als "zwischen" den beiden Reihen stehend. Auch die Beobachtung, dass der Siedepunkt von VII, $n = 8$ stärker als üblich von der Destillationsgeschwindigkeit abhängt, stützt die Vermutung, dass hier neben der *cis*-Konfiguration schon eine *Gleichgewichtskonzentration der leichter flüchtigen* trans-*Form* auftritt. Unter der Annahme, dass *cis*-Heptanolid das gleiche elektrische Moment besitzt wie *cis*-Hexanolid, errechnet sich aus dem gefundenen Moment ein 25 proz. Anteil der *trans*-Konfiguration.

Das *Octanolid* (*VII*, $n = 9$) weist sich durch seinen Siedepunkt als Glied der *trans*-Reihe aus. Lediglich die spezif. Verseifungsgeschwindigkeit ist noch viel zu gross. Im Rahmen des dynam. Gleichgewichts würde die Gegenwart von 6–10% cis-*Lacton* sowohl der Hydrolysenkonstante als auch dem Dipolmoment Rechnung tragen.

Beim *Nonanolid* (VII, $n = 10$) lässt die sehr kleine Verseifungskonstante keinen Zweifel an der ausschliesslichen *trans*-Konfiguration. Die Erhöhung des Dipolmoments um 0·15*D* gegenüber dem erst bei VII, $n = 12$ erreichten Standardwert

[41] J. F. Eijkman, *Chem. Weekblad* **1**, 421 (1904); **2**, 229 (1905); **4**, 191, 727 (1907); H. Beyer, *Ber. Dtsch. Chem. Ges.* **70**, 1101 (1937); R. T. Arnold, J. S. Buckley und J. Richter, *J. Amer. Chem. Soc.* **69**, 2322 (1947); R. V. Christian, *Ibid.* **74**, 1591 (1952); W. L. Mosby, *Ibid.* **74**, 2564 (1952); *J. Org. Chem.* **19**, 294 (1954); W. E. Truce und C. E. Olson, *J. Amer. Chem. Soc.* **74**, 4721 (1952); D. D. Phillips, *Ibid.* **77**, 3658 (1955).

[42] VII, $n = 4$;[19] VII, $n = 6$: F. Fichter und A. Beisswenger, *Ber. Dtsch. Chem. Ges.* **36**, 1200 (1903); VII, $n = 7$: F. J. van Natta, J. W. Hell und W. H. Carothers, *J. Amer. Chem. Soc.* **56**, 455 (1934).

1·86 *D* muss somit auf eine *Winkeldeformation* der *trans*-Carbonestergruppe zurückgehen.

In der Betrachtung am Molekülmodell aus Stuart–Briegleb-Kalotten (Fig. 6 und 7) erweist sich VII, $n = 9$ als das kleinste, leidlich spannungsfrei realisierbare *trans*-Lacton; bei VII, $n = 8$ lässt sich die *trans*-Konfiguration nur mit Winkeldeformation erkaufen. Angesichts des beachtlichen Energieunterschieds zwischen

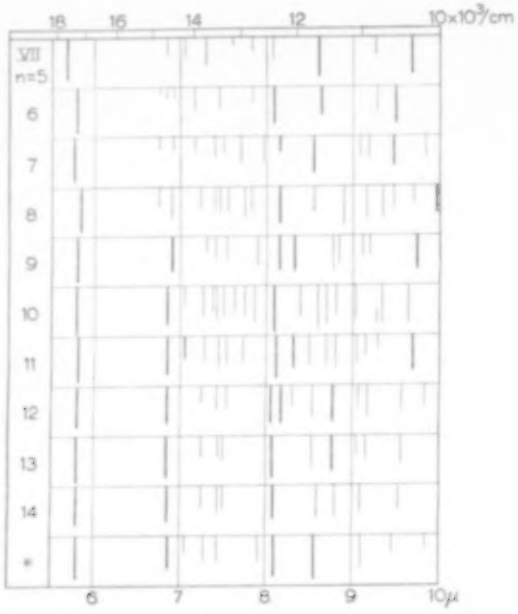


FIG. 8. Strichdiagramm der IR-Filmspektren der ω-Lactone.

cis- und *trans*-Carbonester erscheint es aber plausibel, dass bei VII, $n = 8$ schon eine "schlechte", d.h. *winkeldeformierte trans*-Form mit dem *cis*-Lacton konkurrieren kann (Tabelle 4).

In der strukturell verwandten Reihe der aliphatischen ω-Lactame (III) tritt erst bei $n = 9$ der konfigurative "Übergang" zutage. Vor allem die IR-Spektren lehren, dass III, $n = 9$ im Kristall schon vollständig *trans*-konfiguriert ist, während in der Chloroformlösung 10–15% *trans*- neben der hier noch begünstigten *cis*-Form vorliegen.[6]

Leider leisten die *IR-Spektren der Lactone* keinen erheblichen Beitrag zur Konfigurationsfrage. Abgesehen von der bekannten Sonderstellung des γ-Lactons zeigen die Carbonylfrequenzen im Strichdiagramm der Fig. 8 keinen Gang in Abhängigkeit von der Ringgrösse. Die 10–16-gliedrigen *trans*-Lactone weisen bei 8·1 μ eine starke Bande auf, die wohl der Valenzschwingung der Einfachbindung zwischen Carbonylkohlenstoff und "Äthersauerstoff" zuzuschreiben ist[43] und sich häufig bereits mit der langwelligeren breiten Bande der zweiten CO-Einfachbindung überlappt. Da es kein "Normalspektrum" der *cis*-Lactone in diesem Bereich gibt, gelang die Auflösung

[43] H. W. Thompson und P. Torkington, *J. Chem. Soc.* 640 (1945).

VOL. 6 1959

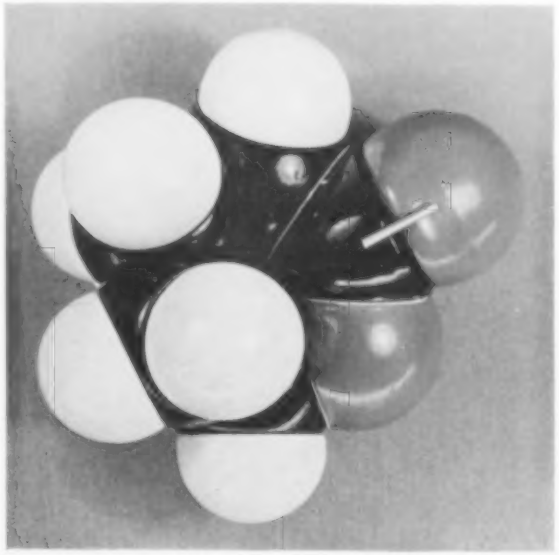


FIG. 6

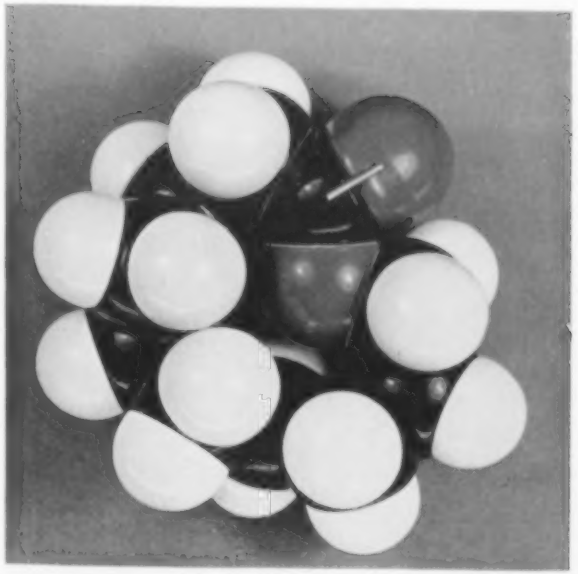


FIG. 7

Molekülmodelle von VII, $n = 6$ und $n = 12$ aus Stuart–Briegleb–Kalotten.

und Zuordnung bei den besonders bandenreichen IR-Spektren der Übergangsglieder nicht.

Gleichgewichte geometrisch-isomerer Formen sollten in ihrer Lage temperaturabhängig sein. Tatsächlich zeigen die bei −70° aufgenommenen IR-Spektren der "Übergangslactone" einige Unterschiede gegenüber den Raumtemperatur-Spektren.[44] Jedoch sind diese nicht so signifikant, dass eine quantitative Auswertung und Interpretation möglich wäre.

Wenngleich somit keine der geprüften physikalischen Methoden den exakten Nachweis des *Nebeneinanders* von *cis*- und *trans*-Konfiguration bei VII, $n = 8, 9$ gestattet, bevorzugen wir diese Hypothese eines dynamischen Gleichgewichts vor der Interpretation mit winkeldeformierten, aber *einheitlichen* Esterkonfigurationen.

VOL. 6 1959

EXPERIMENTELLER TEIL

Darstellung der ω-Lactone

δ-Valerolacton (VII, $n = 6$): Die katalyt. Dehydrierung des 1 : 5-Pentandiols mit Kupfer–Chromoxyd[45] erwies sich am vorteilhaftesten. Nach Entfernung restlichen Diols mittels Phenyl*iso*cyanat und mehrfacher Fraktionierung wurde ein bei 97–98°/10 Torr übergehendes Präparat erhalten, dessen Säureäquivalent bei der Behandlung mit methanolischer Natronlauge und Rücktitration zu 100·7 (Mol. gew. 100·1) gefunden wurde.

ε-Caprolacton (VII, $n = 7$): Oxydation des *Cyclo*hexanons nach Friess[11] mit 74% Ausbeute. Nach wiederholter Destillation ergab die Äquivalenttitration 115·0 (Mol. gew. 114·1); Schmp. −5°. Die Behandlung mit Hydrazinhydrat lieferte 97% d. Th. *ε-Hydroxy-capronsäure-hydrazid* mit Schmp. 114·5–116° (116·5–117·5°[7]).

Heptanolid (VII, $n = 8$): In einer Lösung von 6·2 g *Cyclo*heptanon (55 mMol) in 80 cc Methylenchlorid wurden 35 g feingepulv. trockenes Na_2HPO_4 suspendiert. Unter Eiskühlung und energischem Rühren liessen wir 65 mMol Pertrifluoressigsäure[17] in 50 cc Methylenchlorid innerhalb 30 Min. eintropfen. Nach weiteren 3 Stdn Rühren bei 0° und 3 Stdn bei 20° waren 4·5 mMol Persäure unverbraucht. Nach Absaugen wurde die Methylenchloridphase mit Natriumhydrogencarbonat und Wasser gewaschen. Nach Vertreiben des Solvens gingen bei 76–8°/11 Torr 4·8 g farbl. Öl über; die Äquiv.titration wies auf 92-proz. Lacton. Die Empfindlichkeit des Heptanolids duldet eine Reinigung mit Girards Reagens T nicht. Nach Vereinigung mit den Produkten mehrerer Ansätze gab die fraktionierte Destillation das reine Lacton mit Sdp. 80–82°/11 Torr. Der Geruch ist dem des ε-Caprolactons ähnlich. ($C_7H_{12}O_2$: (128·2) Ber. C, 65·59; H, 9·44; Gef. C, 65·43; H, 9·07; Säureäquiv. gef. 126·7).

0·52 g Heptanolid lieferten mit Hydrazinhydrat 0·65 g *ζ-Hydroxy-önanthsäure-hydrazid* mit Schmp. 118–120°; nach Umlösen aus Essigester Schmp. 122–123° wie ein aus ζ-Brom-önanthsäure bereitetes Präparat.

Aus dem Rückstand der Heptanolid-Destillation (0·92 g) wurden beim Digerieren mit Methanol 0·42 g farbl. Kristalle mit Schmp. 99–100° erhalten, die beim Erhitzen verpufften. ($C_{14}H_{24}O_4$: (256·4) Ber. C, 65·59; H, 9·44; Gef. C, 65·62; H, 9·30; Mol. gew. (Rast): 234).

Die Mischprobe mit einem Präparat des noch nicht beschriebenen VIII, auf anderem Wege[46] bereitet, gab keine Depression.

Octanolid (VIII, $n = 9$): 12·6 g *Cyclo*octanon (100 mMol) gaben bei der analogen Umsetzung mit 128 mMol Pertrifluoressigsäure 10·2 g rohes Lacton, das noch 4% Unverseifbares enthielt. 10·0 g in 100 cc Methanol wurden mit 4·0 g Girards Reagens T und 7·6 cc Eisessig 2 Stdn rückflussgekocht und nach Erkalten mit 400 cc Wasser, die 6·3 g Soda enthielten, verdünnt. Das mit Äther wie üblich aufgearbeitete, farbl. Lacton zeigte Sdp. 72–73°/11 Torr. ($C_9H_{14}O_2$: (142·2) Ber. C, 67·57; H, 9·93; Gef. C, 68·08; H, 9·92; Säureäquiv. gef. 141·1).

[44] Für die Aufnahme der Tieftemperaturspektren sowie für die Diskussion der IR-Spektren sind wir Herrn Dr. E. Bickert und Frl. Köhler, Max-Planck-Institut für Biochemie, München, zu aufrichtigem Dank verpflichtet.

[45] J. G. M. Brenner und D. G. Jones, Engl. Pat. 583 344 (*Imp. Chem. Ind. Ltd.*); *Chem. Zentralbl.* I, 404 (1948); L. E. Schniepp und H. H. Geller, *J. Amer. Chem. Soc.* **69**, 1545 (1947).

[46] W. Dilthey, M. Inckel und H. Stephan, *J. Prakt. Chem.*[2] **154**, 219 (1940).

0·40 g Lacton ergaben bei der Hydrazinolyse 96% d.Th. eines bei 126–128° schmelzenden *ω-Hydroxy-caprylsäure-hydrazids;* das aus Essigester umgelöste Präparat schmolz wie ein authentisches bei 131–132°.

Lactone VII, $n = 9$–16: Die Cylisierung der ω-Brom-fettsäuren[47] mit Kaliumcarbonat[48] wurde in der früher bei anderen Ringschlüssen in hoher Verdünnung bewährten Apparatur[49] ausgeführt. Die Lacton-Ausbeuten entsprachen den beschriebenen.[16] Aus dem Rückstand der Destillation des Nonanolids (VII, $n = 10$) wurden mit Methanol 19% d.Th. am dimeren Lacton (20-gliedr. Ring) mit Schmp. 57–58° isoliert (Lit.[12] 56–57°) ($C_{18}H_{32}O_4$: (312·4) Ber. C, 69·19; H, 10·32; Gef. C, 69·26; H 10·17%).

Bei der Darstellung der höheren Homologen traten die dimeren Lactone nicht mehr auf. Als wirksamste Reinigung von VII, $n = 9$–16 erwies sich die Tieftemperaturkristallisation aus dem 2–4 fachen Volumen Methanol.

Bestimmung der Dipolmomente

Apparatur, Messung der Dielektrizitätskonstante, Dichtebestimmung und Auswertung schlossen sich eng an die früher für aliphatische Lactame gegebene Beschreibung[5] an. Der Dielektrizitätskonstanten–Molenbruch–Funktion wurden für jedes Lacton 5–12 Messungen mit verschiedenen Konzentrationen ($\gamma_2 = 0{\cdot}0008$–$0{\cdot}019$) zugrundegelegt. Diese streng linearen Funktionen ermöglichten eine Reproduzierbarkeit des Dipolmoments innerhalb $\pm 0{\cdot}02D$. Die im gleichen Molenbruch ebenfalls lineare Dichte-Funktion wurde mit pyknometrischen Messungen an jeweils 4 Konzentrationen festgelegt. Anstelle der ganzen Zahlentabellen sei nur ein Beispiel wiedergegeben (VII $n = 6$):

DK-Messung		Dichtebestimmung	
$\gamma_2 \times 10^3$	ε	$\gamma_2 \times 10^3$	d
1·906	2·3207	5·592	0·87509
3·846	2·3686	9·639	0·87612
6·233	2·4276	13·411	0·87711
8·127	2·4742	15·551	0·87767
10·057	2·5212		
12·732	2·5861		

Kinetik der alkalischen Lacton–Hydrolyse in 60-proz. Dioxan

Die Arbeitsweise sei an einem Beispiel skizziert: 317·3 mg Dodecanolid (1,600 mMol) wurden in einer dünnwandigen Glaskugel von 1 cm Durchmesser durch ein Kapillarrohr aufgesaugt und abgeschmolzen. Im Reaktionsgefäss, einem 100 cc Kjeldahlkolben mit seitlichem Ansatz für das Durchleiten CO_2-freier Luft während des ganzen Versuchs, wurden 1·600 mMol CO_2-freier Natronlauge in 50 cc Dioxan-Wasser (60 : 40 Vol%) thermostatisiert; das Dioxan war zuvor durch Rückflusskochen über Natrium und Feinfraktionierung gereinigt worden. Die Hydrolyse wurde durch Zertrümmern der Ampulle gestartet; der Zertrümmerungsapparat wurde sodann entfernt und das Gefäss mit einem durchbohrten Korkstopfen mit locker eingeführter Pipette verschlossen. Zu definierten Zeiten liessen wir 5 cc Proben in jeweils 25 cc eiskaltes, säurefreies Aceton einfliessen, was einer Löschung der Hydrolyse gleichkam. Unverzüglich, vor der Aufnahme nennenswerter Mengen Luftkohlensäure, wurde der Laugenüberschuss mit $n/30$ Salzsäure gegen Phenolphthalein titriert. Mit 9 Proben à 5 cc pflegten wir die Reaktion bis zu 40-70 proz.Umsatz zu verfolgen.

Das Gesamtvolumen wurde bei Raumtemp. abgemessen. Die Volumenausdehnung des Solvens beim Erwärmen auf die Messtemperatur findet sich bei den Konzentrationsangaben berücksichtigt.

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[49] R. Huisgen, W. Rapp, I. Ugi, H. Walz und I. Glogger, *Liebigs Ann.* **586**, 52 (1954).

Die Auswertung erfolgte, wie üblich für die Reaktion zweiter Ordnung mit gleichen Anfangskonzentrationen, graphisch im Diagramm $1/C-1/C_0$ gegen t. 3 Messungen am Dodecanolid mögen in Fig. 9 als Beispiel dienen. Alle Messungen wurden doppelt, bzw. bei mangelnder Übereinstimmung der RG-Konstanten häufiger ausgeführt. Die RG-Konstanten für VII, $n = 9$–16 waren innerhalb $\pm 1\%$, die von VII, $n = 5$, 7, 8 innerhalb $\pm 2\%$ reproduzierbar. Aus den RG-Konstanten bei 3 Temperaturen wurden nach Arrhenius die Aktivierungsenergien mit Fehlern $< \pm 0{\cdot}2$ kcal ermittelt.

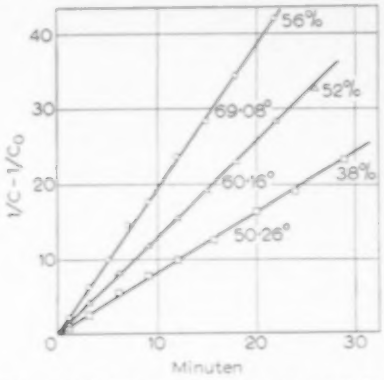

FIG. 9. Kinetik der alkalischen Hydrolyse von VII, $n = 13$ bei 3 Temperaturen. Die Prozentangabe bezieht sich auf den Umsatz beim letzten Messpunkt.

Lediglich die Verfolgung der raschen Hydrolyse des δ-Valerolactons (VII, $n = 6$) bedurfte einer Änderung der Methode. Hier war für jeden Messpunkt eine eigene Ampulle mit Einwaage erforderlich. Die bei 0° durchgeführte Umsetzung musste nach 5–25 Sek. durch Eingiessen von auf −50° gekühltem Aceton gelöscht werden. Die aus 11 Messpunkten algebraisch ermittelten *RG*-Konstanten zeigten eine Streuung von $\pm 20\%$.

Exaltolid (VII, $n = 16$) ist schwerer löslich als die niederen Homologen. Hier wurde in 100 cc Volumen mit 10 cc Proben gearbeitet.

Die Deutsche Forschungsgemeinschaft und der Fonds der Chemischen Industrie unterstützten das Arbeitsprogramm dankenswerterweise mit Sachbeihilfen. H.Ott dankt dem Fonds der Chemischen Industrie sowie der Max-Buchner-Forschungsstiftung der Dechema für Studienbeihilfen. Herrn Dr. I.Ugi, München, schulden wir für seine Hilfe bei den dielektrischen Messungen, Frl. I. Ziegler für die Aufnahme der IR-Spektren und die Dichtebestimmungen Dank.

VOL. 6 1959

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BOOK REVIEW

JOHN T. EDSALL and JEFFRIES WYMAN: **Biophysical Chemistry.** Vol. 1. **Thermodynamics, Electrostatics and the Biological Significance of the Properties of Matter.** Academic Press, New York, 1958. XV 699 pp., $14.00.

THIS book has grown out of a course given at Harvard in the physical chemistry of biochemical systems; it contains accounts of a number of aspects of biophysical chemistry. The authors have deliberately chosen to treat a limited number of subjects very deeply rather than to attempt a complete treatise. The emphasis is on broad general principles and no attempt has been made to provide comprehensive tabulations of experimental data such as are to be found in COHN and EDSALL's *Proteins, Amino Acids and Peptides*. In some ways this is a pity since it is now 15 years since COHN and EDSALL's monograph appeared, in which time a great deal of new material has become available.

The present work starts with a chapter called "Biochemistry and Geochemistry" in which the distribution of chemical elements in living organisms and in the earth's crust is discussed, together with sections on the early history of the earth, the ocean and the central importance of carbon in biology. This is followed by a chapter devoted to that most important substance, water. The next chapter is called "Problems of Protein Structure"; it contains lucid descriptions of many of the modern methods employed in this field, and of the results obtained with them.

Chap. 4 is entitled "Thermodynamics", it extends over 100 pp, of which nearly 70 are devoted to an account of the fundamental ideas of thermodynamics which might well be considered outside the scope of such a book, being more suitable to a text on physical chemistry. The latter part of this chapter is largely concerned with the application of thermodynamics to a number of biological systems. Then follow chapters on electrostatics, dielectric constants and conductivity of electrolytes in which are developed in detail the theory of electrolytic solutions, with particular reference to solutions of dipolar ions. Acid-base equilibria are considered *in extenso* in Chap. 8 and in the next chapter there is a most valuable and interesting account of polybasic acids, bases and ampholytes which includes both proteins and synthetic polyelectrolytes. There follows, somewhat curiously, a chapter devoted to carbon dioxide and carbonic acid which one cannot help feeling would have found its place more naturally in Vol. 2, which will be called *Physical Chemistry of Macromolecules and of Blood*. The last chapter in the present volume contains an excellent account of molecular interactions with particular reference to binding of ions to polyelectrolytes, though it is a pity that such protein–protein interactions as the interaction of antigens with antibodies are not discussed in any detail.

It is impossible to express an opinion on this book as a whole without being able to read Vol. 2, thus there are a number of topics which the present reviewer would have liked to see treated but which may well be found in the next volume. One thing in particular is the lack of any account of kinetics without which no work on biophysical chemistry can be anything like complete. The authors mention this deficiency in the preface and hold out some hope that they will cover the subject in some future volume, it is to be hoped that they will be able to do so. The production is throughout of a high standard and the equations, however complex, are all printed very clearly though some of the symbols used appear strange. Thus ω is used to denote ionic strength instead of μ, which is general in the American literature. There is no doubt, however, that this is a most excellent book which will be the constant companion of biophysical chemists for many years to come and one looks forward eagerly to the publication of Vol. 2.

S. P. DATTA

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SELECTIVE REACTIONS AND MODIFICATION OF FUNCTIONAL GROUPS IN STEROID CHEMISTRY

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INTRODUCTION

THE last ten years have seen a concentrated effort in the partial and total synthesis of steroids, occasioned in particular by the discovery of the adrenocortical hormones and of their physiological activity. This effort has involved conducting selective reactions on multifunctional compounds, and protection of one type of functional group against the consequence of reactions aimed at another. It seems desirable to give a review of such selective reactions and modifications; not only for the benefit of workers in the steroid field itself, but also as a guide for those working in other fields of organic synthesis, some of whom tend to assume that steroid chemistry is an exclusive domain.

This review covers the more important literature from 1948 through 1957, but it is not intended to be exhaustive. Work on tricyclic intermediates in steroid total synthesis has been included, but facts published in communication form are not dealt with unless such communications mention a modicum of experimental detail.

A. SELECTIVE REACTIONS OF C—C DOUBLE BONDS

1. *Selective catalytic reduction of* C—C *double bonds*

(a) *Isolated and* C—C *conjugated double bonds.* Apart from double bonds at the 8:14- (and hence at the 7-) position, which are reduced catalytically only under extreme conditions,[1,2] the isolated C_5 double bond is relatively the most unreactive to hydrogenation. It is unaffected when double bonds at positions 16, 17(20) and 20, or triple bonds (for instance in a 17-ethinyl group) are saturated in the presence of palladium catalysts.[3] In the presence of platinum it can be hydrogenated, usually in the presence of acids, giving an A/B-*trans*-steroid, except in the case of 3α-substituted pregn-5-enes which are reported to give normal (A/B-*cis*) pregnanes,[4] and, analogously, *epi*cholesterol, whose hydrogenation gives *epi*coprostanol.[5] The steric course of hydrogenation of Δ^4- and Δ^5-steroids in general has been explained on the basis of conformational arguments.[6]

An isolated C_{14} double bond appears to be slightly less reactive to hydrogenation than one at C_5;[7] its saturation usually gives the normal 14α-configuration.

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Side chain double bonds (e.g. at the 22(23)-position) are next in order of susceptibility to catalytic hydrogenation, and this can often be effected with Raney nickel catalysts in cases where the $\Delta^7 \rightarrow \Delta^{8(14)}$ shift, which occurs with palladium, and with platinum in acidic (though not in neutral) media,[8] is undesirable. The acid catalysed $\Delta^{8(14)} \rightarrow \Delta^{14}$ migration does not occur in certain cases.[9]

Double bonds at C_6 or $C_{8(14)}$ in maleic anhydride adducts of 5:7- or 7:14-dienes are not affected when a side chain double bond is hydrogenated.[10] The stepwise and selective reduction of 5α:8α-epidioxides of 5:7-dienes, of importance in the production of 5α-hydroxy ergostane- and -cholestane derivatives, has been described in detail.[11,12]

A C_7-double bond in 9β*H*-steroids can be catalytically reduced even before one in the side chain.[13–15] Steric influences are also evident in the behaviour of the 9(11)-double bond, which is inert to hydrogenation in A/B-*cis*-steroids,[16] but less so in A/B-*trans*-steroids.

Turning to selective hydrogenation of C=C-conjugated double bonds: a 5:7:9(11):22(23)-tetraene is generally reduced in the order: $\Delta^5 > \Delta^{9(11)} > \Delta^{22(23)} > \Delta^7 (\rightarrow \Delta^{8(14)})$, using Raney nickel[17–21] or copper chromite[22] catalysts, less advantageously with palladium or platinum.[23,24] In conjugated diene systems represented by enol ethers or enol acetates of α:β-unsaturated ketones the γ:δ-double bond can be selectively hydrogenated using palladium,[25–28] giving an A/B-*trans*-junction if it is at the 5-position.

Selective catalytic reductions in unsaturated 3:5-*cyclo*steroids have been described.[1,29] (Table 1.)

(b) *Systems containing carbonyl conjugated double bonds.* Selectivity in catalytic hydrogenation in these systems depends to a large extent on the catalyst and solvent employed; and for this reason a relatively large number of examples are given.

It is reported that double bonds at C_{16} (including Δ^{16}-20-ketones), $C_{17(20)}$, C_{20}, and ethinyl groups at C_{17} can be hydrogenated with palladium catalysts under neutral or slightly alkaline conditions before a Δ^4-3-ketone is reduced.[3] In other cases the presence of pyridine favours the selective reduction of a carbonyl conjugated

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(b). J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton and G. H. Thomas, *J. Chem. Soc.* 2921 (1953).
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VOL. 6 1959

TABLE 1. EXAMPLES

Compound	Conditions	Double bond reduced at	Ref.
3β-Acetoxy 17-methyl androsta-5:16-diene and -5:17(20)-diene	Pd/C, EtOH	16 or 17(20) [17β-configuration]	30
3β-Acetoxy 17-methyl androsta-5:16-diene	Pd/C, EtOH	16 [17β-configuration]	31
3β-Acetoxy 17-keto 13-*iso* androsta-5:14-diene	Pt, HOAc	5[17-hydroxy]	7
Zymosterol [8(9):22(23)-diene]	RaNi, Benz	22	32
3β-Hydroxy cholesta-5:7-diene	RaNi, Dioxan	5	18
3-Ethylenedioxy cholesta-5:7-diene	RaNi, EtOH, Et_2O	5	33
3β:17β-Diacetoxy androsta-5:7-diene	Pt, EtOAc	5	34
3β-Acetoxy cholesta-6:8(9)-diene	Pt, EtOAc	6 (no shift of $C_{8(9)}$ double bond)	2
3β-Acetoxy 22a-spirosta-5:7-diene	Pt, EtOAc	5	9, 24
3β-Acetoxy 22a-spirosta-5:7-diene	RaNi, Dioxan	5	36
3-Ethylenedioxy 22a-spirosta-5:7-diene	RaNi	5	35
Ergosterol acetate [5:7:22(23)-triene]	RaNi, Benz.	5	17, 20, 36
Ergosterol acetate [5:7:22(23)-triene]	CuCrO	5	22
3β-Acetoxy ergosta-7:9(11):22(23)-triene	CuCrO	9	22
3β-Acetoxy ergosta-7:9(11):22(23)-triene	RaNi, Xyl.	9, 22	22
3β-Acetoxy ergosta-7:9(11):22(23)-triene	RaNi, EtOAc	9, 22	19
3β-Acetoxy ergosta-7:9(11):22(23)-triene	Pt, EtOAc	9, 22	36
3β-Acetoxy ergosta-6:8(14):22(23)-triene	RaNi, Dioxan	6	20
3β-Acetoxy ergosta-8(14):22(23)-diene	Pt, Dioxan	22	20
3β-Benzoyloxy ergosta-5:7:14:22(23)-tetraene	Pt, Et_2O, HOAc	5, 14, 22 [giving Δ-8(14)]	10
Methyl 3β-acetoxy bisnorchola-5:7-dienate	RaNi, Benz.	5	36
3β-Acetoxy 7-keto ergosta-9(11):22(23)-diene	Pd/C, EtOAc, HOAc	9, 22	37

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over an isolated double bond. Catalytic reduction of a Δ^{16}-20-ketone and reduction of a 14:16-diene-20-ketone with sodium and propanol, or lithium and liquid ammonia[38] leads to the normal 17β-configuration, but total catalytic reduction of 14:16-dienes[39,40] or of 14:15-epoxy 16-enes[39] leads to 14β:17α-steroids.

Catalytic reduction of Δ^4-3-ketones usually affords a mixture of products containing an A/B-*cis*- and A/B-*trans*-junction;[41-42] a trace of alkali increases the proportion of the former. However, hydrogenation of 11β-hydroxy and 11-oxo Δ^4-3-ketones leads to an A/B-*trans*-steroid,[41,43] and the A/B-*trans*-junction is always formed on reduction of Δ^4-3-ketones with metals in liquid ammonia, with or without a proton donor.

The resistance of the C_7-double bond to hydrogenation extends even to the case of a Δ^7-6-ketone,[44] while $\Delta^{8(9)}$-7-ketones and $\Delta^{8(9)}$-7:11-diketones can be reduced both catalytically and with zinc and acetic acid to give the normal (9αH:8βH) B/C-ring-junction.[37] This is of interest in connexion with the report that catalytic reduction of $\Delta^{8(9)}$-11-ketones gives an 8αH:9αH-steroid,[45] even in case where the C/D-ring-junction is *cis*.[46]

A number of remarkably specific catalytic hydrogenations in synthetic intermediates have been described, and some are shown in the examples given.[47-50] (Table 2.)

TABLE 2. EXAMPLES

Compound	Conditions	Double bond reduced at	Ref.
Androstane derivatives			
3β-hydroxy, 17-one, 16-methylene, 5-ene	Pd/C, EtOH	16-methylene	51
[17β-hydroxy, 17α-vinyl or -ethinyl, 3-one, 4-ene	Li/NH_3	4 in both cases (A/B *trans*)	52]
3β-acetoxy, 17-ethoxycarbonyl, 5:14:16-triene	$Pd/CaCO_3$, EtOH	14, 16 (17α, 14βH)	39
3-one, 17-ethoxycarbonyl, 4:9(11):16-triene	$Pd/SrCO_3$	4, 16 (mixture of A/B-*cis* and *trans*)	50
3-one, 17-formyl, 4:9(11):16-triene	$Pd/SrCO_3$, *i*-PrOH	16	48
Pregnane derivatives			
3α-acetoxy, 20-one, 7:16-diene	Pd/EtOAc, Piperidine	16	53
(*allo*) 3β-acetoxy, 20-one, 7:16-diene	Pd/EtOAc, Piperidine	16	54
(*allo*) 3β-acetoxy, 20-one, 8(14):16-diene	Pd/C, EtOAc	16	9

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TABLE 2 (*contd.*)

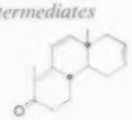
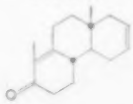
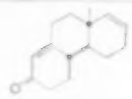
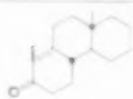
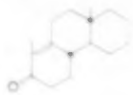
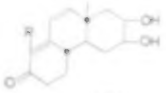
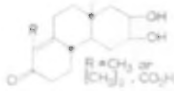
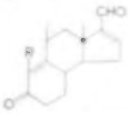
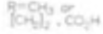
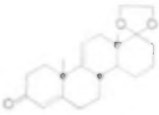
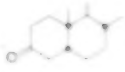
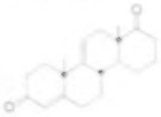
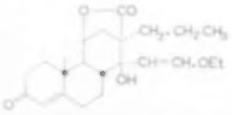
Compound	Conditions	Double bond reduced at	Ref.
(*allo*) 3β-acetoxy, 20-one, 9(11):16-diene	Pd/C, EtOAc	16	55
1β:3β-dihydroxy, 20-one, 5:16-diene	Pd/C, EtOAc	16	56
3β-acetoxy, 6-methyl, 20-one 5:16-diene	Pd/$CaCO_3$, MeOH	16	57
3β-acetoxy, 12:20-dione, 5:16-diene	Pd/$BaSO_4$, EtOAc, 45°	16	58
3β-acetoxy, 12:20-dione, 5:16-diene	Pt, HOAc	5, 16	59
21-acetoxy, 3-ethylenedioxy, 20-one, 18β → 11β-lactone, 5:16-diene	Pd/$CaCO_3$, EtOH	16	60
Ergostane derivatives			
3β-acetoxy, 7-one, 8(9):22(23)-diene	Pd/C, EtOAc	22	37
3β-acetoxy, 7:11-dione, 5:22(23)-diene	Pd/C, HOAc	5, 22	37
3β-acetoxy, 5α-hydroxy, 6-one, 7:22(23)-diene	Pd/C, dioxan, EtOH	22	44
3-one, 4:6:22(23)-triene [*iso*ergosterone]	Pd/$SrCO_3$, benz.	6	61
3-one, 4:6:22(23)-triene [*iso*ergosterone]	Pd/C, KOH, EtOH	4, 6 (A/B *cis*)	61, 62
3-one, 4:6:22(23)-triene [*iso*ergosterone]	Pd/C, KOH, EtOH (smaller concentration of OH^-)	6	62, 63
[3-one, 4:6:22(23)-triene [*iso*ergosterone]]	Li/NH_3, MeOH	6	[62]
3β-acetoxy, 7-one, 5:8(9):22(23)-triene	RaNi, EtOAc	5, 22	37
3β-acetoxy, 7-one, 5:8(9):22(23)-triene	Pd/C, EtOAc, HOAc	5, 8, 22	37
[3β-acetoxy, 7:11-dione, 8(9):22(23)-diene	Zn, HOAc	8	[64]
3β-acetoxy, 7-one, 5:9(11):22(23)-triene	Pd/C, HOAc	5, 22	37
3β-acetoxy, 5α-hydroxy, 6-one, 7:14:22(23)-triene	Pd/$CaCO_3$, benz.	14, 22	44
3β-acetoxy, 5α-hydroxy, 6-one, 7:9(11):22(23)-triene	Pd/$CaCO_3$, benz.	9, 22	44
[3β:5α-diol, 6-one, 7:9(11):22(23)-triene	Li/NH_3	7, 9, 6-one → 6α-hydroxy 5α-hydroxy → 5α-H	[44]
22a-*Spirostane derivatives*			
3-one, 4:7-diene	Pd, dioxan, KOH	4 (A/B *cis*)	53
3-one, 4:7:9(11)-triene	Pd, EtOH, KOH	4 (A/B *cis*)	65
3-one, 4:6:8(9)-triene	Pd, EtOH, KOH	4, 6 (A/B *cis*)	66
Synthetic intermediates		*Product*	
	Pd/$SrCO_3$, *i*-PrOH, NaOH		47

TABLE 2 (*contd.*)

Compound	Conditions	Double bond reduced at	Ref.
	Pd, EtOAc		49
	Pd, EtOAc		49
	$Pd/SrCO_3$, Benz.		50
	$Pd/SrCO_3$, *i*-PrOH, NaOH		48
	$Pd/SrCO_3$, *i*-PrOH,		48
			
	Pd, KOH		67
	Pd, KOH		67
	Pd, EtOH, Py		60

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(c) *Compounds containing acetylenic linkages.* It seems to be possible to effect partial or even total saturation of an 17-ethinyl group[3] before a 4-ene 3-ketone group is reduced. The opposite result can be achieved by metal/ammonia reduction, in which the ethinyl group is protected by its metal derivative. (Table 3.)

TABLE 3. EXAMPLES

Compound	Conditions	Group reduced	Ref.
17β-Hydroxy 3-keto 17α-ethinyl androst-4-ene	$Pd/CaCO_3$, Py	17-ethinyl [→ vinyl]	3
17β-Hydroxy 3-keto 17α-ethinyl 19-*nor*androst-4-ene	$Pd/CaCO_3$, Py	17-ethinyl [→ vinyl]	68
17β-Hydroxy 3-keto 17α-ethinyl androst-4-ene	Pd/C, dioxan	17-ethinyl [→ ethyl]	3
17β-Hydroxy 3-keto 17α-ethinyl androst-4-ene	Li/NH_3	4-ene (A/B *trans*)	52
3β-Acetoxy 17β-hydroxy 17α-ethoxyethinyl androst-5-ene	$Pd/CaCO_3$, Py	17-ethoxyethinyl [→ ethoxyvinyl]	69

(d) *Miscellaneous selective catalytic hydrogenations.* Catalytic reduction of the double bond in a Δ^4-3-ketone can be avoided by formation of its ethylene glycol ketal and resulting shift of the double bond to the 5-position,[70] for example in the catalytic debromination of a 16β:17α-bromohydrin.[71] On the other hand a Δ^4-3-ketone can be reduced catalytically to the saturated ketone (Pd, dioxan, KOH; A/B-*cis*) without affecting a 16:17α-epoxide;[72] the latter can be hydrogenolysed without saturation of an isolated double bond with sodium and an alcohol.[73]

A double bond at position 5 is unaffected during catalytic hydrogenolysis (Pd/C EtOH) of a 16α-benzyloxy group.[74]

The selective catalytic hydrogenation of the γ-δ double bond in α:β:γ:δ doubly unsaturated ketones[47,48,50,61–62] is paralleled by the selective hydrogenolysis of the epoxide ring in an α-β-unsaturated γ:δ-epoxy ketone ($Pd/SrCO_3$, *i*-PrOH, KOH; or Zn, HOAc).[75]

II. *Selective epoxidation of double bonds*

Many examples of selective epoxidation have been described, particularly in work on compounds related to ergosterol in connexion with the introduction of an 11-oxygen function. The often complicated reactions attendant on and subsequent to epoxidation of 7:9(11)-dienes (with both mild and strong peracids) have been adequately reviewed.[76,77,81] Outstanding features, however, are: (i) the resistance of

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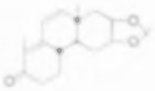
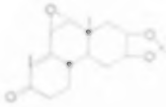
TABLE 4. EXAMPLES

Compound	Conditions	Product	Ref.
Ergostane derivatives			
3:5-*cyclo*, 8(14):22-diene	Excess perbenz.	8:14α-epoxide	1
3β:5α-diacetoxy, 7:9(11)-diene	Perphthal., Et_2O 1·1 mol	9:11α-epoxide	78
3β:5α-diacetoxy, 7:9(11)-diene	Perform.	7:8α, 9:11α-diepoxide	78
3β-acetoxy, 7-one, 9(11):22-diene	Perphthal.,	9:11α-epoxide	37
3β-acetoxy, 5:7:22(23)-triene [ergosteryl acetate]	Perbenz. or perphthal:	complex mixture	87, 88
3β-acetoxy, 7:9(11):22-triene	Perbenz. or perphthal.	(successively): 9:11α-mono, 7:8α, 9:11α-di and 7:8α, 9:11α, 22:23-triepoxide	89 64, 90, 91
3β-5α-diol, 7:9(11):22(23)-triene	Perphthal.	9:11α-epoxide	92
3β-acetoxy, 5α-ol, 6-one, 7:14:22(23)-triene	Perphthal.	14:15-epoxide [low yd.]	44
3β:5α-diol, 6-one, 7:9(11):22(23)-triene	Perphthal.	9:11α- 22:23-diepoxide	44
Other compounds			
3β-Acetoxy 20-keto *allo*pregna-7:9(11)-diene	Perform.	9:11α-epoxy 7-ketone [no attack on 20-ketone]	78 93
Methyl 3α-acetoxy chola-7:9(11)-dienate	Perphthal.	9:11α-epoxide	90
Methyl 3β-acetoxy allochola-6:9(11)-dienate 5:8α-maleic ester adduct	Perphthal.	9:11α-epoxide	94
3β:5α:22-Triacetoxy bisnorchola-7:9(11):20(22)-triene	Perphthal.	9:11α-epoxide	78
3β-Acetoxy, 5α-hydroxy *allo*-spirosta-7:9(11)-diene	Perphthal.	(successively) 9:11α-epoxide and 7:8α, 9:11α-diepoxide	95
Carbonyl conjugated double bonds			
17-Formyl 3:11-diketo androsta-4:16-diene	H_2O_2, NaOH MeOH	16:17α-epoxide	80
17-Formyl 3-keto androsta-4:9(11):16-triene	H_2O_2, NaOH, MeOH	16:17α-epoxide	80
	Perphthal.		75
Enol acetates			
20-Acetoxy 3-keto-pregna-4:17(20)-diene	Perbenz.	17α-Hydroxy pregn-4-ene 3:20-dione	96
3β:11:20-Triacetoxy pregna-9(11):17(20)-diene	Perbenz.	17α-ol-20-one	82
3:20-Diacetoxy pregna-3:5:20(21)-triene	Perbenz. (1 mole)	*allo*pregnane 3:6:20-trione	84
3:20-Diacetoxy pregna-3:5:20(21)-triene	Perbenz. (2 moles)	17α-hydroxy *allo*-pregnane 3:6:20-trione	84

the 22(23)-double bond to epoxidation, and (ii) the initial formation of the 9:11α-epoxide from 7:9(11)-dienes in both A/B-*cis*- and A/B-*trans*-steroids (even in the case of a 7:9(11):20(22)-trien-22-ol acetate).[78] Examples have been chosen from cases where additional functional groups might be liable to introduce a complicating factor.

Carbonyl-conjugated double bonds are generally unaffected by electrophilic epoxidation (exception[79]), but can be epoxidised with hydrogen peroxide and alkali. It appears possible in this to differentiate between a ketone-conjugated and aldehyde-conjugated double bond,[80] the latter being more easily attacked.

Some detailed work has been done on the selective epoxidation of compounds containing several enol acetate groupings in connexion with the introduction of the cortical side chain,[77,81] particularly such as are derived from pregnane-[82] and *allo*-pregnane-11:20-diones.[83] Of special interest are: (i) the selective epoxidation at Δ^{16} of 16:20(21)-dien-20-ol acetates,[84] (ii) the reaction of 3:5-dien-3-ol acetates with peracids[85] and (iii) the differential behaviour of 20:21-epoxy- and of 17:20-epoxy-20-ol acetates on heating or chromatography on silica.[86] (Table 4.)

III. *Selective hydroxylation of double bonds*

Work in this field has concentrated mainly on the hydroxylation of double bonds at C_{16} and $C_{17(20)}$, in connexion with the construction of the cortical side chain. The C_5-double bond appears to be relatively inert to the reagents generally used (osmium tetroxide or potassium permanganate), however ergosterol can be selectively hydroxylated to give a 5:6-glycol.[88] As with epoxidation, attack of hydroxylating agents is generally from the "rear" of the steroid molecule, but of interest in this connexion are: (i) the "front attack" of osmium tetroxide on a Δ^5-3-glycol ketal to give the 5β-6β-glycol[97] and on Δ^3-cholenic acid to give the 3β:4β-diol,[165] and (ii) the different *cis*-glycols obtained by the action of osmium tetroxide and the Prévost reagent (silver acetate and iodine in wet acetic acid).[47,50,98]

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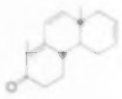
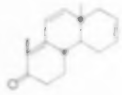
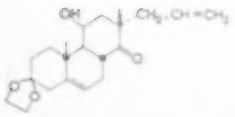
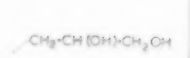
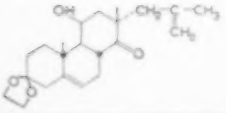
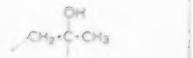
[96] C. Djerassi, J. Grossman and G. H. Thomas, *J. Amer. Chem. Soc.* **77**, 3826 (1955).
[97] S. Bernstein, W. S. Allen, C. E. Linden and J. Clementi, *J. Amer. Chem. Soc.* **77**, 6612 (1955).
[98] H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.* **78**, 3749 (1956).

TABLE 5. EXAMPLES

Compound	Reagent	Product	Ref.
Pregnane derivatives			
3β-acetoxy, 20-one, 5:16-diene	OsO_4	16:17α-diol [osmate could be rearranged to D-homosteroid]	101
3β-acetoxy, 20-one, 5:16-diene	$KMnO_4$, acetone, HOAc	16:17α-diol	102
21-acetoxy 3-one, 4:17(20)-diene	H_2O_2, trace of OsO_4	20-one 17α-ol	103
3:20-dione, 4:16-diene	OsO_4	16:17α-diol	101
3β:21-diacetoxy, 20-one, 5:16-diene	$KMnO_4$, acetone, HOAc	16:17α-diol	104
3β:21-diacetoxy, 20-cyano, 5:17(20)-diene	$KMnO_4$, acetone, HOAc	20-one-17α-ol and further oxidation products	105
21-acetoxy, 3-one, 20-cyano, 9(11):17(20)-diene	OsO_4	20-one-17α-ol [In the corresp. *allo* compound, $\Delta^{9(11)}$ is also attacked]	106 107
21-acetoxy, 3-ethylenedioxy, 11-one, 20-cyano, 5:17(20)-diene	$KMnO_4$, acetone, piperidine	20-one-17α-ol	108
21-acetoxy, 3:20-dione, 5:9(11):16-triene	OsO_4	16:17α-diol [HOBr was then added to $\Delta^{9(11)}$]	109
21-acetoxy, 11β-ol, 3-one, 4:17(20)-diene	phenyl iodosoacetate OsO_4	20-one-17α-ol	110, 111
Other compounds			
Ergosterol	$KMnO_4$, methyl cyclohexane, water, 90–100°	5:6α-diol	88
	Silver acetate, iodine, HOAc, H_2O		48
	OsO_4		50
	Silver acetate, iodine HOAc, H_2O		47
	OsO_4		112
	OsO_4		113

Double bonds at the 9(11)-position are inert in A/B-*cis*-steroids[99] and in 5α:8α-epidioxyergostane derivatives,[100] but are hydroxylated in the A/B-*trans*-series, as is observed with epoxidation and electrophilic attack in general. (Table 5.)

IV. *Selective ozonisation of double bonds*

In contrast to peracids and hydrogen in the presence of catalysts, ozone will in most cases attack specifically a side chain, as against a cyclic, double bond. This applies both to isolated and enol acetate double bonds. Selectivity, and improved yields of resulting side chain aldehydes and -ketones have been found to be enhanced considerably by the presence of pyridine[63,114,115] and by conducting the ozonisation at as low a temperature as possible.[62,78,115,116] (Table 6.)

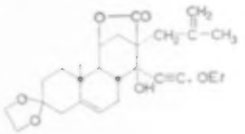
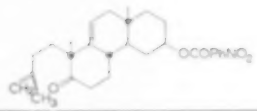
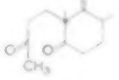
B. MODIFICATION OF DOUBLE BONDS

I. *By halogen addition*

It appears that bromine or chlorine addition to double bonds (for protection against oxidation) does not always differentiate between isolated nuclear and side chain double bonds, at least in compounds related to ergosterol, even though the selective addition of these reagents,[120] as well as of hydrogen chloride[121] to the C_5 double bond in stigmasterol has been reported. However, it seems that regeneration of double bonds from their dihalides is more selective. It has been shown[122,123] that sodium iodide (in acetone) will regenerate a nuclear double bond from its dibromide, leaving a 22:23-dihalide, from which the double bond is regenerated only with zinc in acetic acid. 22:23-Dihalides are stable also to catalytic hydrogenation conditions,[15] though not in the presence of alkali.[124]

[99] D. Gould, E. L. Shapiro, H. L. Herzog, M. J. Gentles, E. B. Hershberg, W. Charney, M. Gilmore, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *J. Amer. Chem. Soc.* **79**, 502 (1957).
[100] R. B. Clayton, A. Crawshaw, H. B. Henbest, E. R. H. Jones, B. J. Lovell and G. W. Wood, *J. Chem. Soc.* 2009 (1953).
[101] G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.* 4377 (1955).
[102] G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.* 4373 (1955).
[103] K. Miescher and J. Schmidlin, *Helv. Chim. Acta* **33**, 1840 (1950).
[104] B. Ellis, F. Hartley, V. Petrow and D. Wedlake, *J. Chem. Soc.* 4383 (1955).
[105] J. Heer and K. Miescher, *Helv. Chim. Acta* **34**, 259 (1951).
[106] R. P. Graber, A. C. Haven and N. L. Wendler, *J. Amer. Chem. Soc.* **75**, 4722 (1953).
[107] R. Hirschmann, C. S. Snoddy and N. L. Wendler, *J. Amer. Chem. Soc.* **75**, 3252 (1953).
[108] G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, *J. Amer. Chem. Soc.* **76**, 5031 (1954).
[109] S. Bernstein, R. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *J. Amer. Chem. Soc.* **78**, 5693 (1956).
[110] J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, *J. Amer. Chem. Soc.* **77**, 4436 (1955).
[111] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Amer. Chem. Soc.* **78**, 6213 (1956).
[112] G. I. Poos and L. H. Sarett, *J. Amer. Chem. Soc.* **78**, 4100 (1956).
[113] L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, *J. Amer. Chem. Soc.* **75**, 2112 (1953).
[114] J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta* **40**, 1438 (1957).
[115] G. Slomp and J. L. Johnson, *Abstracts ACS* 129th meeting, 30N (1956).
[116] P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood and G. F. Woods, *J. Chem. Soc.* 4890 (1952).
[117] R. B. Moffett and D. I. Weisblatt, *J. Amer. Chem. Soc.* **74**, 2183 (1952).
[118] F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.* **72**, 2617 (1950).
[119] G. Stork, H. J. E. Loewenthal and P. C. Mukerdji, *J. Amer. Chem. Soc.* **78**, 501 (1956).
[119a] D. H. Hey, J. Honeyman and W. J. Peal, *J. Chem. Soc.* 2881 (1950).
[120] H. Q. Smith and E. S. Wallis, *J. Org. Chem.* **19**, 1628 (1954).
[121] E. M. Chamberlin, E. Tristram, T. Utne and J. M. Chemerda, *J. Amer. Chem. Soc.* **79**, 456 (1957).
[122] J. A. McEwan and F. S. Spring, *J. Chem. Soc.* 3646 (1952).
[123] J. Paterson and F. S. Spring, *J. Chem. Soc.* 325 (1954).
[124] R. Budziarek, R. Stevenson and F. S. Spring, *J. Chem. Soc.* 4874 (1952).

TABLE 6. EXAMPLES

Compound	Conditions	Product	Ref.
Fucosterol		24-ketocholesterol	119a
Stigmasta-4:22-dien-3-one	Py (1 mole), methylene chloride, −78°	side chain aldehyde	115
Ergosta-4:22-dien-3-one	methylene chloride, Py −70°	side chain aldehyde	63
Ergosta-6:9(11):22-triene, 5:8-maleic anhydride	2 equivs. O_2	side chain acid	94
3β:5α-Diacetoxy 9:11α-epoxy ergosta-7:22-diene	EtOAc, −70°	side chain aldehyde	78
3β-Acetoxy 5:8α-epidioxy- ergosta-9(11):22-diene	EtOAc, −70°	side chain aldehyde and -acid	116
Enol acetates			
3β:21-Diacetoxy pregna-6:9(11):20(21):triene 5:8-maleic ester adduct	Methylene chloride	17-carboxylic acid	117
Mixture of enol acetates from 3-keto bisnorchol-4-en-22-al	$CHCl_3$	Progesterone	118
Enol acetate of			
3β:5α-Diacetoxy 9:11α-epoxy bisnorchol-7-en-22-al	EtOAc, −70°	20-ketone	78
3β-Acetoxy 5:8α-epidioxy bisnorchol-9(11)-en-22-al	EtOAc, −70°	20-ketone	116
3β-Acetoxy bisnorchol-5-en-22-al	$CHCl_3$	20-ketone	118
Miscellaneous			
	Py, $CHCl_3$		114
	Methylene chloride, −20°		119

Complications may ensue in the presence of ketone or α:β-unsaturated ketone groups. A carbonyl-conjugated double bond adds bromine less readily than an isolated double bond, especially in the presence of acetate ion,[105,125–128] but in the presence of a saturated 20-ketone α-keto bromination appears to be unavoidable.[120,130]

[115] R. K. Callow and D. A. H. Taylor, *J. Chem. Soc.* 2299 (1952).
[116] H. Heusser, E. V. Jensen, N. Frick and P. A. Plattner, *Helv. Chim. Acta* **32**, 1326 (1949).
[117] H. H. Inhoffen, F. Blomeyer and K. Brueckner, *Chem. Ber.* **87**, 593 (1954).
[118] B. Loeken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 1738 (1956).
[119] P. L. Julian and W. J. Karpel, *J. Amer. Chem. Soc.* **72**, 362 (1950).
[120] J. Romo and A. Romo de Vivar, *J. Amer. Chem. Soc.* **79**, 1118 (1957).

II. *By other methods*

Reversible 3:5-*cyclo*steroid formation, applicable to 5-ene-3-ols, has been used occasionally to protect both the 3β-hydroxy group and the C_5-double bond against oxidation and epoxidation, usually in the form of 6-methoxy *i*-steroids.[57,79,131–134]

Nitration of the C_5-double bond in stigmasterol has been used for its protection during ozonolysis of the side chain double bond; the nitroethylene group was subsequently reduced to the 6-ketone.[120]

It has been suggested[98] that a suitable form of protection of a double bond might be the diester or acetonide of a *cis*-glycol, which may be reconverted to the olefin by treating its ditosylate or dimesylate with sodium iodide. This sequence has been employed in 2:3-dihydroxysapogenins,[98,135–137] where it appears that the last step is applicable to the dimesylates of 2α:3α- and 2α:3β-diols, but not 2β:3β- or 2β:3α-diols.[98]

The double bond in α:β-unsaturated ketones can be protected as the epoxide (formed with hydrogen peroxide and alkali) from which its regeneration is possible by mild reduction with chromous ion.[138] The possibility of protecting other types of double bonds as epoxides and their regeneration by reaction with triphenylphosphine[139] is attractive but as yet unexplored.

C. SELECTIVE REACTIONS OF CARBONYL GROUPS

I. *Selective reduction*

The order of selective reduction of steroid ketones by metal hydrides, in particular sodium borohydride, has been summarised and exemplified by a number of authors.[140–142] It is stated to be: 3- > 17- or 20- > Δ^4-3- > 11-ketones, both in A/B-*cis*- and A/B-*trans*-steroids. It has been pointed out that this order is paralleled by that of decreasing oxidation potentials of simple alicyclic analogues of such ketones.[141]

However, a relatively minor change in general stereochemistry may affect this sequence: the selective sodium borohydride reduction of 8-*iso*androst-4-ene 3:17-dione was unsuccessful.[143]

Selectivity in reductions with borohydrides appears to be substantially increased in the presence of pyridine.[72,142,144,145]

Catalytic reduction, at any rate with nickel catalysts, appears to follow the same order as with borohydrides, though selectivity is generally less and dependent on the

[131] D. H. Hey, J. Honeyman and W. J. Peal, *J. Chem. Soc.* 4836 (1952).
[132] P. L. Julian, E. W. Meyer and H. C. Printy, *J. Amer. Chem. Soc.* **70**, 887 (1948).
[133] W. J. Peal, *J. Chem. Soc.* 3801 (1957).
[134] B. Riegel, E. W. Meyer and J. Beiswanger, *J. Amer. Chem. Soc.* **65**, 325 (1943).
[135] C. Djerassi and J. Fishman, *J. Amer. Chem. Soc.* **77**, 4291 (1955).
[136] C. Djerassi, T. T. Grossnickle and L. B. High, *J. Amer. Chem. Soc.* **78**, 3166 (1956).
[137] N. L. Wendler, H. L. Slates and M. Tishler, *J. Amer. Chem. Soc.* **74**, 4894 (1952).
[138] W. Cole and P. L. Julian, *J. Org. Chem.* **19**, 131 (1954).
[139] G. Wittig, *Experientia* **12**, 41 (1956).
[140] E. Elisberg, H. van der Haeghe and T. F. Gallagher, *J. Amer. Chem. Soc.* **74**, 2814 (1952).
[141] J. K. Norymberski and G. F. Woods, *J. Chem. Soc.* 3426 (1955).
[142] A. H. Soloway, A. S. Deutsch and T. F. Gallagher, *J. Amer. Chem. Soc.* **75**, 2356 (1953).
[143] C. Djerassi, H. Bendas and A. Segaloff, *J. Org. Chem.* **21**, 1056 (1956).
[144] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1286 (1953).
[145] O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **74**, 3711 (1952).

state of the catalyst.[146] Platinum or palladium catalysts seem to have been employed only when one of the ketone groups is highly hindered, this is illustrated by some interesting work on tricyclic intermediates.[147,148] Meerwein-Ponndorf reduction appears to affect only saturated and unhindered ketones.[149,150] Wolff-Kischner reduction reduces all except 11-ketones under the ordinary Huang-Minlon conditions;[89,151–153] the 11-keto group can be reduced by a special procedure involving a completely anhydrous environment.[154]

The stereospecificity of the reduction of ketones to alcohols has been studied in detail. An earlier review[149] has generalised that with metal hydrides an unhindered ketone gives the equatorial and a hindered ketone the axial alcohol; Meerwein-Ponndorf reduction yields a larger proportion of the axial epimer,[155,156] while catalytic reduction gives the axial alcohol in acidic and the equatorial alcohol in neutral or basic media. Later work has led to the following conclusions: Reduction with sodium borohydride follows "steric control" to give a greater proportion of the axial epimer (in this connexion the formation of the 7α-alcohol from 7-keto cholanic acid[157] is of interest), while with lithium aluminium hydride "product control" giving the equatorial epimer predominates.[158] A comparison of products obtained by lithium aluminium hydride and catalytic reduction has also been made: with 4-, 6-, 7- and 11-ketones the same epimer ratio is obtained by both methods; with 2-, 3-, or 12-ketones it may vary according to the method used.[159]

11-Ketones on reduction with metal hydrides give mainly the 11β-(axial)alcohol,[160] though with lithium borohydride some of the 11α-epimer is formed;[161] this is given preponderantly on reduction with sodium and alcohols or with alkali metals and liquid ammonia in the presence of a proton donor.[160,162,163] From 20-ketones the 20β-alcohol is the main product of reduction by nearly all methods; the 20α-epimer is obtained on reduction of Δ^{16}-20-ketones or 16α:17α-epoxy-20-ketones with sodium and alcohols or with lithium aluminium hydride.[164]

In the borohydride reduction of keto esters in alcoholic solution ester exchange is always a possibility.[165] (Table 7.)

II. *Selective enol acetate formation*

Enol acetylation affects mainly α:β-unsaturated and unhindered ketones, roughly in that order. A further degree of selectivity is provided by the use of different

[146] C. Djerassi, A. J. Manson and M. Gorman, *J. Amer. Chem. Soc.* **77**, 4925 (1955).
[147] P. A. Robins and J. Walker, *J. Chem. Soc.* 642 (1952).
[148] P. A. Robins and J. Walker, *J. Chem. Soc.* 3960 (1954).
[149] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).
[150] P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta* **36**, 376 (1953).
[151] L. F. Fieser, W. Huang and J. C. Babcock, *J. Amer. Chem. Soc.* **75**, 116 (1953).
[152] Huang-Minlon, *J. Amer. Chem. Soc.* **71**, 3301 (1949).
[153] F. Sondheimer, E. Batres and G. Rosenkranz, *J. Org. Chem.* **22**, 1090 (1957).
[154] D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.* 2056 (1955).
[155] J. Elks and G. H. Phillips, *J. Chem. Soc.* 4320 (1956).
[156] H. R. Nace and G. L. O'Connor, *J. Amer. Chem. Soc.* **73**, 5824 (1951).
[157] E. H. Mosbach, W. Meyer and F. E. Kendall, *J. Amer. Chem. Soc.* **76**, 5799 (1954).
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[160] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **75**, 1282 (1953).
[161] E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Amer. Chem. Soc.* **76**, 6111 (1954).
[162] H. L. Herzog, M. Jevnik and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 269 (1953).
[163] H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, *J. Amer. Chem. Soc.* **74**, 4470 (1952).
[164] E. L. Shapiro, D. Gould and E. B. Hershberg, *J. Amer. Chem. Soc.* **77**, 2912 (1955).
[165] K. Yamasaki, V. Rosnati, M. Fieser and L. F. Fieser, *J. Amer. Chem. Soc.* **77**, 3308 (1955).

TABLE 7. EXAMPLES

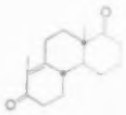
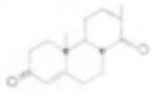
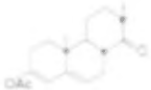
Functional groups	Method	Product	Ref.
Androstane derivatives			
3:17-dione	$NaBH_4$	3β-ol	140
5β-H, 3:17-dione	$NaBH_4$	3α-ol	140
3:17-dione	Deactivated RaNi	3α-(50%) and 3β-(34%) ol	146
5β-H, 3-ethylenedioxy, 11:17-dione	Pt, Py	17β-ol	166
Pregnane derivatives			
(*allo*) 3:20-dione	$NaBH_4$/Py	3β-ol	142
3:20-dione	$NaBH_4$	3α-ol	4
3α-acetoxy, 11:20-dione	Pt	20β-ol	168, 169
3α-hydroxy, 11:20-dione	Pt	20-ol (both epimers)	170
(*allo*) 20β-acetoxy, 3:16-dione	Pt	3β-ol	171
11α-acetoxy, 3:20-dione	$NaBH_4$	3α-ol [kinetics studied]	172
3α:17α-diol, 11:20-dione	Pt, Py	20β-ol	166
3α-acetoxy, 17α-ol, 11:20-dione	Pt, HOAc	20β-ol	173
3α:17α-diol, 11:20-dione	$NaBH_4$	20β-ol	174
3β:17β-diol, 11:20-dione	$NaBH_4$, reflux	11β:20β-diol	174
3α-ol, 21-benzylidene, 11:20-dione	KBH_4	3α:20β-diol	161
3α-ol, 21-benzylidene, 11:20-dione	$LiBH_4$	3α:11β:20α-triol and 3α:11α:20α-triol	161
3α-ol, 21-benzylidene, 11:20-dione	$LiAlH_4$	21-benzyl 3α:11β:20α-triol	161
(*allo*) 11β:17α-diol, 21-acetoxy, 3:20-dione	RaNi, dioxan	3β-ol	42
3:11:20-trione	$NaBH_4$, Py	3α-ol	142, 144, 145
3:11:20-trione	$NaBH_4$, EtOH	3α-20β-diol	145
(*allo*) 3:11:20-trione	RaNi	3β-ol	175, 176
(*allo*) 3:11:20-trione	$NaBH_4$, Py	3β-ol	142
17α-ol, 3:11:20-trione	$NaBH_4$, aq. Py	3α-ol	72
21-acetoxy, 17α-ol, 1:4-diene, 3:11:20-trione	$NaBH_4$	20β-ol	177
Other compounds			
3β-Acetoxyergosta-22-ene 7:11-dione	Meerwein-Ponndorf	7β-ol	155
3β-Acetoxyergosta-22-ene 7:11-dione	Alc. KOH	7α-ol	155
Allo-22a-Spirost-8(9)-ene 3:7:11-trione	RaNi	3β-ol	178
Synthetic intermediates			
	Meerwein-Ponndorf		179
	$LiAlH_4$ (on enol ether of unsatd. ketone)		150

TABLE 8. EXAMPLES

Functional groups	Conditions	Product	Ref.
Pregnane derivatives			
3α-ol, 11:20-dione	Ac_2O, sulphosalicylic acid, toluene, 12 hr	17(20)-ene, 3:20-diacetate	184
3α-ol 11:20-dione	Ac_2O, sulphosalicylic acid, toluene, 25 min	3α-acetate only	184
3α-ol, 11:20-dione	Ac_2O, TsOH, no solvent	9(11):17(20)-diene 3α:11:20-triacetate	184 185, 186
(*allo*) 3β-acetoxy, 11:20-dione	Ac_2O, CCl_4, $HClO_4$	17(20)-ene 20-acetate	83
3β-acetoxy, 8(9)-ene, 7:20-dione	*iso*Propenyl acetate, TsOH, Benz.	7(8):9(11)-diene 7-acetate	187
(*allo*) 21-acetoxy, 17α-ol, 3:20-dione	Ac_2O, sulphosalicyclic acid, toluene	2-ene 3-acetate	188
21-acetoxy, 17α-ol, 3:11:20-trione	Ac_2O, sulphosalicyclic acid, toluene	3-ene 3-acetate	188
Other compounds			
Methyl 3α-acetoxy 7:12-diketo cholanate	Ac_2O, TsOH	6-ene 7-acetate	181, 182
3β-acetoxy 11-oxo bisnor*allo*cholanal	Ac_2O, NaOAc	20(22)-ene 22-acetate	180
3β-acetoxy 11-oxo bisnor*allo*cholanal	Ac_2O, $HClO_4$, CCl_4	(aldehyde diacetate)	180
Bisnorcholan-22-al-3-one	Ac_2O, NaOAc	20(22)-ene 20-acetate	62
	AcCl, Ac_2O		189

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reagents: *iso*propenyl acetate is milder than acetic anhydride in the presence of sulphonic acid catalysts, but in general results appear to be capricious or dependent on small variations in experimental technique. The course of enol acetylation of 20-keto steroids, of importance in the construction of the cortical side chain, has been adequately described.[81]

In many cases lack of selectivity in enol acetylation is compensated for by selectivity in subsequent epoxidation (see section A.II).

More detailed quantitative studies have shown that *iso*propenyl acetate reacts mainly with α:β-unsaturated ketones as against saturated 20-ketones.[93] The selective enol acetylation at the 20-keto group of an *allo*pregnane 11:20-dione has been examined in detail (in this case carbon tetrachloride, acetic anhydride and 50% perchloric acid as catalyst have been found to be optimum conditions).[83]

Aldehyde groups are converted into enol acetates even with acetic anhydride in the presence of sodium acetate.[62,180] The enol acetate of a 7-ketone has the double bond at C_6.[181,182] The 12-ketone group does not give an enol acetate.[117] (Table 8.)

The $\Delta^{3(5),5,17(20)}$-dienol acetate of progesterone reacts selectively at the 5-double bond with N-iodo succinimide;[96] from the resulting 6-iodo 4-ene 3-ketone the 17(20)-en-20-ol acetate could be obtained by reduction with sodium bisulphite.

III. *Reaction at α-keto carbanions*

Progesterone can be dialkylated in the 4-position (methyl iodide, potassium *tert.* butoxide), without affecting the 20-ketone group.[190]

On the other hand, acylations by esters occur preferentially at anions of saturated ketone groups. Thus, progesterone with one molar equivalent of ethyl oxalate gives only the 21-oxalyl ester,[190] the same is observed with 11-keto progesterone[110,111] (in the latter case excess of acylating ester gave the 2:21-dioxalyl ester, in which, after bromination, a Favorskii rearrangement was obtained only in the side chain). An 11- or potential 11-ketone group (as in synthetic intermediates) is unaffected when ketone groups at other positions are acylated.[191,192] Of interest are two examples of tricyclic synthetic intermediates, in which acylation occured next to an unsaturated, rather than a saturated ketone group.[179,193]

IV. *Nucleophilic attack on ketone groups*

Unsaturated ketone groups appear to be less attacked by sodium or potassium acetylides than saturated ketones[194] though protection of the former by enol ether or ketal formation is advantageous in this reaction.[195] The selective Knoevenagel reaction at a 3-ketone group with cyanoacetic ester in the case of ethyl dehydrocholate has been reported.[196] The 11-keto group in methyl 3α-acetoxy 11-keto cholanate is inert to Grignard reagents, to the extent that Barbier-Wieland degradation of the ester group is possible without complications.[64]

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V. *Electrophilic attack on ketone groups*

In 11:17-diketones the 17-keto group can be attacked selectively by peracids, to give a single or mixture of ring D lactones.[197–199] In *allo*pregn-16-ene 12:20:dione peracids give the C-lactone 16:17α-epoxide;[200] 11-ketone groups are inert to peracids while 12-ketones appear to give only a single ring C lactone.[201] The selective formation of bis-hydroperoxides of 3- and 12-ketones, by the action of dry hydrogen peroxide, has been described.[202]

VI. *Selective halogenation of ketones*

The selective bromination of ketone groups appears to be governed mainly by their accessability. Thus, 3-ketones in both the normal and *allo* series can be mono- and even dibrominated before 11-ketones,[43,64,82,203] 12-ketones,[204–206] 17-ketones[143,161,207,208] or 20-ketones[62,203,209–212] are affected. The course of bromination of 3-ketones in A/B-*cis*- and *trans*-steroids has been described in detail.[25,213] 20-Ketones on dibromination give the 17α:21-dibromo derivatives.[129,203,209]

Oestrone can be selectively iodinated in the aromatic ring, using iodine and mercuric acetate in acetic acid.[214] α-Keto bromination in this case,[215] and in the case of ketones containing an isolated double bond[117] is best done through the enol acetate. In fact, where selective direct formation of a α-halo ketone fails, addition of hypohalous acid to the double bond of a selectively formed enol acetate (see Section B.II) may be successful.

The dehalogenation of halo 3-ketones[212] and of 17:21-dibromo-20-ketones[129] has been discussed in general terms.

VII. *Miscellaneous reactions*

Steroid 3-ketones can be selectively converted to 3-methoxy compounds by catalytic reduction in methanol containing hydrogen bromide.[216]

The remarkably specific action of selenium dioxide in *tert.* butanol on 3-ketones and Δ^4-3-ketones, to give 1:4-diene-3-ketones, without affecting ketone groups at other positions or the cortical side chain, has been reported by a number of

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workers,[174,217,218] though some of their results have been disproved to a certain extent.[219]

D. MODIFICATION OF CARBONYL GROUPS

1. *By glycol ketal formation*

Protection of ketonic groups by ketal formation with ethylene or other glycols is one of the important aspects of steroid chemistry. Such ketals are stable to practically every kind of basic environment, including Huang-Minlon reduction[220] and the strongly alkaline conditions needed to hydrolyse a tertiary ester group,[221] (where the presence of a free ketone group led to the destruction of the molecule). They are however cleaved by base yielding ethylene glycol enol ethers in cases where they become part of a vinylogous β-diketone system.[222,223]

By choosing appropriate mild conditions ketal groups are ordinarily unaffected by acylating agents in pyridine, such as acetic anhydride,[224] acetyl chloride,[225] *p*-toluenesulphonyl chloride,[225,226] methanesulphonyl chloride;[227] and by dehydrating agents such as phosphorus oxychloride[108,228–230,233] and thionyl chloride (generally below 0°).[231,232] They are stable to organic peracids under suitable conditions,[111,233] to osmium tetroxide,[97,225,235] and to periodic acid in the presence of pyridine.[113,225,226,235]

Suitable conditions (usually with oxalic acid) have been found for the selective cleavage of enol ethers, such as obtained by Birch reduction of aromatic ethers,[234,236] and even for the rearrangement of an ethoxyethinyl carbinol (with dilute mineral acids in the presence of tetrahydrofuran or dioxan as Lewis bases),[237] without affecting a ketal group. It has been reported[236] that the 3-ethylene glycol ketal of 16-methoxycarbonyl androst-4-ene 3:17-dione was cleaved by aqueous dioxan at 200°; in this case the β-keto ester could be decarbomethoxylated (without affecting the ketal) by heating in *p*-cymene.

Ketals have been shown to be reasonably stable to conditions used for enol lactone formation (refluxing in acetic anhydride),[48,67] and to N-bromosuccinimide, preferably in the presence of potassium carbonate.[33,222,238] Even mercuric acetate dehydrogenation in acetic acid[35] and oxidations with *tert.* butyl chromate (entailing

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treatment with acetic and oxalic acids)[223] can be carried out in their presence. If hindered (for example as the 3-monoketal of a 4-chloro-3:20-diketopregnane) they can survive bromination (at C_{21}) with bromine in chloroform.[239,240] They are unaffected by the chromic acid-pyridine complex.[113,119,195]

Apart from their obvious use as protecting groups ketals have found use in shifting the easily reducible double bond in a Δ^4-3-ketone to the difficultly reducible C_5-position.[71] An interesting use is described in the synthesis of 14-*iso*oestrone methyl ether, during which a 16-bromo 17-ketone was dehydrobrominated after ketalisation of the ketone group to prevent destruction of the resulting *cyclo*-pentenone group by the base employed.[215] Finally ketalisation has been employed to prevent hemiketal formation between a ketone and a suitably disposed incipient hydroxyl group.[119]

(a) *Selective ketal formation.* Most procedures for ketalisation with ethylene glycol follow the original method of Salmi:[309a] refluxing the ketone in benzene or toluene with excess glycol in the presence of an acid catalyst, with azeotropic removal of the water formed. Some works have used boron trifluoride etherate as catalyst.[241–243] Similar results are reported with propylene glycol.[240]

In general, ease of ketalisation appears to be in the following order: 3-ketone or Δ^4-3-ketone > 17-ketone > 12-ketone > 20-ketone > 17α:21-dihydroxy 20-ketone > 11-ketone and 21-acetoxy 20-ketone.

Among hindered ketones, 4-chloro-3-ketones can still be ketalised[240] while 4:4-dimethyl-3-ketones are reported to be inert.[190] 11-Ketals can be formed in moderate yields by prolonged reaction.[244] In cases where acid sensitive tertiary hydroxyl groups are present ketalisation has been carried out in the glycol in the absence of solvent at 80° with removal of the water formed *in vacuo*.[245,246]

The experimental conditions for ketalisation have been studied in detail in the case of androst-4-ene 3:17-dione:[247] with a low acid catalyst/diketone ratio the 3-ketal is formed preponderantly, while higher ratios favour formation of the 17-ketal.

Increased selectivity of ketalisation is possible by using the method of exchange ketalisation between a steroid ketone and the ketals of acetone or 2-butanone in the presence of acid catalysts.[248] Order of ketalisation by such procedures is quoted as: 3- or 20-ketones > Δ^4-3-ketones > 2- or 4-bromo-3-ketones; no reaction being shown by 17-ketones or 2:4-dibromo-3-ketones. This was found to depend partly on the exact experimental procedure employed, such as: refluxing the ketone with the aliphatic ketal with or without removal (by fractionation) of the aliphatic ketone formed; and with or without the use of additional solvent.

As is well known, ketalisation of a Δ^4-3-ketone causes a shift of the double bond

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[243] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.* 1046 (1957).
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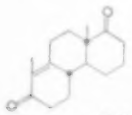
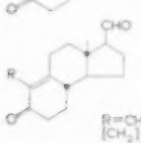
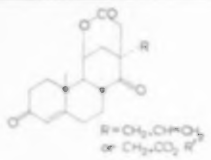
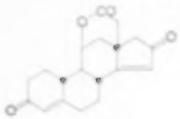
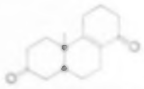
VOL. 6 1959

TABLE 9. EXAMPLES

Compound	Method	Ketal formed at position	Ref.
Androstane derivatives			
4-ene, 3:17-dione	Exchange	3	248
5β-H, 8(9):14-diene, 3:16-dione		3	193
3:6:17-trione	Exchange, 2-butanone ketal: 5 min	3	250
	Exchange, 2-butanone ketal: 30 min	3, 6	250
	Exchange, 2-butanone ketal: 5 hr	3, 6, 17	250
5β-H, 3:11:17-trione	Azeotropic	3, 17	163
5β-H, 3:11:17-trione	Azeotropic (1 mole glycol)	3 [50% yd.]	166
5β-H, 17-carboxyl, 3:11-dione	Glycol, methylene chloride, SeO_2, room temp.	3	251
Pregnane derivatives			
4-ene, 3:20-dione	Exchange (10 min)	3 (25% yd.)	252
4:16-diene, 3:20-dione	Exchange	3	252
3α-acetoxy, 11:20-dione	Azeotropic	20	253
(*allo*) 3β-acetoxy, 12:20-dione	Glycol, BF_3/Et_2O	12	243
4-ene, 21-hydroxy, 3:20-dione	Glycol at 80°, no solvent	3 (and some 3:20-bisketal)	246
4-ene, 21-acetoxy, 3:20-dione	Azeotropic	3	238
5-ene, 4:4-dimethyl, 3:20-dione		20	190
4-ene, 21:21-dibenzyloxy, 3:20-dione	Exchange	3	255
(*allo*) 3β:17α-dihydroxy, 12:20-dione	Glycol, BF_3/Et_2O	12	241
4-ene, 11α:17α:21-trihydroxy, 3:20-dione	Glycol at 80°, no solvent	3, 20	245
4-ene, 3:11:20-trione	Azeotropic	3, 20	256
(*allo*) 17α-hydroxy, 3:12:20-trione	Azeotropic	3, 12	241
4-ene, 21-acetoxy, 3:11:20-trione	Exchange (mesityl oxide ketal)	3	257
4-chloro, 17α-hydroxy, 3:11:70-trione	Azeotropic (ethylene and propylene glycols)	3, 20	240
4-ene, 17α-hydroxy, 21-acetoxy, 3:11:20-trione	Exchange	3	258, 259
Other compounds		*Product*	
	Azeotropic	(No yds. given)	150
 R=CH3 or [CH2]2 · CO2R'	Azeotropic		48

Compound	Method	Product	Ref.
	Azeotropic or Exchange	"3"-ketal	260
	Azeotropic Exchange	3-ketal 3,16-bisketal	260 260
	No conditions given		193

to the C_5-position,[79] but no such shift is observed on ketalisation of Δ^{16}-20-ketones.[249] The ketalisation of unsaturated ketones at other positions does not appear to have been investigated in this respect. (Table 9.)

(b) *Selective cleavage of ketals.* The order of cleavage of glycol ketals appears to be analogous to their order of formation. Thus 3-ketals and Δ^5-3-ketals are those cleaved by the mildest conditions (glacial acetic acid, *p*-toluenesulphonic acid in acetone at room temperature); ketals at other positions are succesively cleaved with aqueous acetic acid, mixtures of acetic and mineral acids and mineral acids in aqueous alcohols. Sometimes ketal cleavage, being more carefully controllable from the point of pH of the medium employed, may be more selective than ketal formation. Occasionally mild conditions have had to be used to prevent elimination of an 11β- or 17α-hydroxyl group.[240,261] (Table 10.)

II. *Dimethyl and diethyl ketals*

The formation of these, by the action of the corresponding alcohols in the presence of acid catalysts, appears to be highly specific to ketones at C_3. Using selenium dioxide as catalyst it has been shown[263] that only saturated 3-ketones form ketals; Δ^4-3-ketones, 11-ketones and 17- or 20-ketones being unaffected. On heating 3:3-dimethyl ketals are reported to form enol ethers.[263] Their formation has been

[79] S. Bernstein, M. Heller and S. M. Stolar, *J. Amer. Chem. Soc.* **76**, 5674 (1954).
[249] G. Rosenkranz, M. Velasco and F. Sondheimer, *J. Amer. Chem. Soc.* **76**, 5024 (1954).
[261] E. P. Oliveto, H. Q. Smith, C. Gerold, R. Rausser and E. B. Hershberg, *J. Amer. Chem. Soc.* **78**, 1414 (1956).
[262] F. Sondheimer, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 192 (1955).
[263] G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.* **17**, 290 (1952).
[264] G. Rosenkranz, O. Mancera, F. Sondheimer and C. Djerassi, *J. Org. Chem.* **21**, 520 (1956).
[265] O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **77**, 5669 (1955).
[266] B. J. Magerlein and R. H. Levin, *J. Amer. Chem. Soc.* **75**, 3654 (1953).
[267] J. M. Constantin, A. C. Haven and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 1716 (1953).
[268] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.* **18**, 70 (1953).
[269] F. Sondheimer, O. Mancera and G. Rosenkranz, *J. Amer. Chem. Soc.* **76**, 5020 (1954)
[260] K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta* **40**, 787 (1957).
[261] G. I. Poos, *J. Amer. Chem. Soc.* **77**, 4932 (1955).
[262] E. P. Oliveto, H. Q. Smith, C. Gerold, L. Weber, R. Rausser and E. B. Hershberg, *J. Amer. Chem. Soc.* **77**, 2224 (1955).
[263] E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Amer. Chem. Soc.* **76**, 6113 (1954).

TABLE 10. EXAMPLES

Compound	Conditions of cleavage	Ketal cleaved at position	Ref.
Pregnane derivatives			
4-bromo, 11β-17α-dihydroxy, 3:20-bisketal	HCl, acetone	20	262
5-ene, 11α:17α-dihydroxy, 3:20-bisketal	TsOH, acetone, room temp.	3	160
5-ene, 11α-17α-dihydroxy 3:20-bisketal	TsOH, acetone, room b.p.	3, 20	160
5:16-diene, 11β:21-dihydroxy, 3:20-bisketal	HOAc	3	231
5:16-diene, 11β:21-dihydroxy, 3:20-bisketal	HOAc, H_2O or H_2SO_4, MeOH	3, 20	231
5-ene, 17α:21-dihydroxy, 11-ketone, 3:20-bisketal	HOAc, H_2O	3	258
5-ene, 21-acetoxy, 17α-hydroxy, 11-ketone, 3:20-bisketal	HOAc, H_2O	3	258
5-ene, 21-acetoxy, 11β:16α:17α-trihydroxy, 3:20-bisketal	HOAc, H_2O	3	228
5-ene, 21-acetoxy, 11β:16α:17α-trihydroxy, 3:20-bisketal	H_2SO_4, H_2O	3, 20	228
4-chloro, 17α-hydroxy, 11-ketone, 3:20-bisketal	H_2SO_4, acetone	20	240

utilised in the bromination at C_{21} of a pregnane 3:20-dione without affecting ring A.[262]

III. *Enol ethers*

Enol ethers, usually prepared by the reaction of ketones with orthoformates in the presence of traces of acid, appear to be selectively formed from α:β-unsaturated ketones, in particular Δ^4-3-ketones.[264–266] They are stable to all basic reaction conditions, for example reactions of other ketonic groups with lithium aluminium hydride, Grignard reagents, reduction with sodium and alcohols, Claisen condensations, and to the very strongly alkaline conditions needed for hydrolysing a tertiary ester.[267] An interesting use of enol ethers of Δ^4-3-ketones is that involving selective catalytic reduction of their C_5-double bond, the product rearranging to a 2-en-3-ol ether with an A/B *trans*-junction.[25,27,43] Their cleavage can be effected under very mild acidic conditions, sometimes even by dissolution in technical chloroform.[268]

IV. *Thioketals*

Thioketals of ketones formed with ethane- or propanedithiols in the presence of mild acid catalysts have been used more as intermediates for reduction of such ketones to methylene groups, rather than as protecting groups. Their formation is

[264] S. Bernstein, R. Lenhard and J. H. Williams, *J. Org. Chem.* **18**, 1166 (1953).
[265] P. L. Julian, E. W. Meyer, W. J. Karpel and W. Cole, *J. Amer. Chem. Soc.* **73**, 1982 (1951).
[266] A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 4117 (1953).
[267] C. R. Engel and G. Just, *Canad. J. Chem.* **33**, 1515 (1955).
[268] D. K. Patel, V. Petrow, R. Royer and I. A. Stuart-Webb, *J. Chem. Soc.* 161 (1952).

often very selective. Boron trifluoride ether complex has been suggested as a very suitable catalyst,[269] its action being mildest in acetic acid solution, while use of the complex itself as solvent gives a more vigorous reaction; thus cholestane 3:6-dione gives the 3-thioketal under the former and the 3:6-*bis*thioketal under the latter conditions. Other catalysts that have been used include zinc chloride and methanolic hydrogen chloride. The use of propanedithiol has been reported to give improved yields.[270] The idea of forming thioketals by exchange with dimethyl dithiolan is said to fail.[271] It has been demonstrated that no shift of the double bond occurs on forming thioketals of Δ^4-3-ketones.[272]

While thioketals appear to be stable to alkali,[273] they are reported to be attacked in certain cases by lithium aluminium hydride.[274] Like glycol ketals they can be cleaved to the original ketone with acids, but non-hydrolytic conditions (cadmium carbonate or mercuric chloride) can also be used.[273]

Specificity of thioketal formation depends not only on the position of the ketone group but also on the type of thiol used. 6-, 7- and 12-ketones form thioketals only with dithiols, 3-, 16- and 17-ketones also with monothiols.[275] (Table 11.)

TABLE 11. EXAMPLES

Compound	Conditions	Thioketal formed at	Ref.
Androst-4-ene 3:17-dione	ethanedithiol, TsOH, HOAc	3	276
Androst-4-ene 11β-ol 3:7-dione	ethanedithiol, TsOH, HOAc	3	276
Androst-4-ene 3:11:17-trione	ethanedithiol, TsOH, HOAc	3	276
Pregn-4-ene 3:20-dione	ethanedithiol, TsOH, HOAc	3	276
Pregnane 3:11:20-trione	ethanedithiol, no solvent, HCl, $-15°$	3, 20	277
3β:17β-Diacetoxyandrostane 7:11-dione	ethanedithiol, no solvent, HCl, 0°	7	278
3β-Acetoxycholestane 7:11-dione	ethanedithiol, no solvent, HCl, 0°	7	278
3β-Acetoxyergost-22-ene 7:11-dione	ethanedithiol, no solvent, HCl, 0°	7	278
Methyl 3α-hydroxy 11:12-diketo cholanate	propanedithiol, MeOH, HCl	12	279
3α-Acetoxy 22a:5β-spirostane 7:11-dione	ethanedithiol, HOAc, HBr	7	280

[269] L. F. Fieser, *J. Amer. Chem. Soc.* **76,** 1945 (1954).
[270] H. Hauptmann and M. Moura-Campos, *J. Amer. Chem. Soc.* **72,** 1405 (1950).
[271] C. Djerassi and M. Gorman, *J. Amer. Chem. Soc.* **75,** 3704 (1953).
[272] H. Hauptmann, *J. Amer. Chem. Soc.* **69,** 562 (1947).
[273] L. Norymberska, J. Norymberski and A. Olalde, *J. Amer. Chem. Soc.* **70,** 1256 (1948).
[274] R. H. Mazur and E. A. Brown, *J. Amer. Chem. Soc.* **77,** 6670 (1955).
[275] H. Hauptmann and M. Moura-Campos, *J. Amer. Chem. Soc.* **74,** 3179 (1952).
[276] J. W. Ralls and B. Riegel, *J. Amer. Chem. Soc.* **76,** 4479 (1954).
[277] A. Ruff and T. Reichstein, *Helv. Chim. Acta* **34,** 70 (1951).
[278] H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger and O. Jeger, *Helv. Chim. Acta* **35,** 295 (1952).
[279] S. Archer, T. R. Lewis, C. M. Martini and M. Jackman, *J. Amer. Chem. Soc.* **76,** 4915 (1954).
[280] G. Rosenkranz, M. Velasco, C. Djerassi and F. Sondheimer, *J. Amer. Chem. Soc.* **75,** 4430 (1953).

V. *Thioenol ethers*

Formation of these, generally with benzyl thiol, appears as with enol ethers to be specific to α-β unsaturated ketones.[179] As catalyst pyridine hydrochloride has been suggested.[281] 1:4-addition of the thiol may occur if the conjugated double bond is not sterically hindered (as with cholest-1-ene-3-one,[281,282]) and may happen exclusively with basic catalysts (e.g. piperidine).

Sulphoxides formed by hydrogen peroxide oxidation of thioenol ethers have been suggested as acid-stable modifications of the ketone group;[281] from these the thioenol ether can be regenerated by reduction with lithium aluminium hydride. However, little use seems to have been made of this method of ketone protection.

VOL. 6 1959

VI. *Hemithioketals*

Some interesting work has been done on this type of ketone group modification. Like glycol ketals, hemithioketals can be prepared by azeotropic removal of water on reaction of the ketone with mercaptoethanol or mercaptopropanol, or by exchange with the corresponding acetone hemithioketal.[271] In 4-ene-3-ketones a shift of the double bond to the 5-position is said to be probable.

Hemithioketals are stable to basic reaction conditions and to the action of lithium aluminium hydride.[274,283] Raney nickel does not cause hydrogenolysis but regenerates the original ketone, this affording a method of ketone protection not involving acid conditions for cleavage.[284]

Hemithioketal formation appears to be less subject to steric hindrance than ethylene glycol ketalisation; this is exemplified by dehydrocholic acid[274] from which a tris-hemithioketal can be formed successfully.

VII. *Enamine formation*

This is another method for the protection of carbonyl groups which is specific to α:β-unsaturated ketones, particularly at C_3,[285–287] depending somewhat on the secondary amine used. Thus: androst-4-ene-3:11:17-trione gave the 3-monoenamine with morpholine and the 3:17-*bis*enamine with pyrrolidine.[288] Aldehyde groups are converted to enamines in preference even to Δ^4-3-ketones.[63,289]

Enamines are usually formed by refluxing the ketone with a secondary cyclic amine in benzene solution and azeotropic removal of the water formed. A catalyst is not necessary. Their stability to lithium aluminium hydride (even in the case of an enamine from a 1:4-diene 3-ketone,[111,285,290,291]) to Grignard reagents[286] and to strong acids[291] makes them attractive alternatives to ketals for ketone protection. They are easily cleaved by aqueous alkali.

[281] J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *J. Amer. Chem. Soc.* **73**, 1528 (1951).
[282] P. A. Plattner, A. Fuerst and H. Els, *Helv. Chim. Acta* **37**, 1399 (1954).
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[284] C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *J. Amer. Chem. Soc.* **74**, 3634 (1952).
[285] M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.* **75**, 5927 (1953).
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[288] F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.* **77**, 488 (1955).
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[291] J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Amer. Chem. Soc.* **78**, 430 (1956).

Enamines have also seen use in view of the preferential oxidisability of their C=C double bond (e.g. in the degradation of *bis*-nor aldehydes,[92]) and as intermediates in a new method for the monoalkylation of ketones.[292]

VIII. *Semicarbazones and other hydrazones*

Semicarbazones have seen use as protecting groups in view of their stability to metal hydride reduction, e.g. with lithium aluminium hydride,[293] sodium- or potassium borohydrides[99,294–296] and lithium borohydride[297–300] and to Oppenauer oxidation conditions[301,302] where they have been employed to prevent reduction and self-condensation of a free ketone group.

The selectivity of semicarbazone formation appears to be less pronounced than that of ketalisation, even though the 11-keto group is inert in all cases. 3-Ketones and 4-ene-3-ketones react preferentially;[99,297,303] 20- and 17α-hydroxy 20-ketones also react reasonably rapidly but Δ^{16}-20-ketones are less reactive.[304] 21-Acetoxy-20-ketones are reported to be more prone to semicarbazone than to ketal formation[293,294,296,298,303,305] in spite of earlier reports to the contrary.[300] In a special case selective semicarbazone formation has been studied with regard to reaction temperature and solvent employed.[306]

Cleavage of semicarbazones has been effected mainly by exchange with pyruvic acid;[294,299,307,308] but other reagents such as nitrous acid[293,295] and acetic anhydride/pyridine[309] have also seen use. At this point the use of semicarbazones for the formation of Δ^4-3-ketones from 4-bromo-3-ketones in the pregnane series should be noted[82,210,303] this can be done in the presence of a 21-bromo 20-ketone grouping.[310] Originally 2:4-dinitrophenylhydrazones,[311] and more recently ethoxycarbonylhydrazones,[312] have been used for this conversion.

Other derivatives which have been explored for ketone protection include oximes[293,305] and hydrazones,[293] but their cleavage to the original ketone appears to be more difficult.

IX. *Cyanohydrins*

Cyanohydrin formation appears promising as a method for the specific protection

[292] G. Stork, R. Terrell and J. Szmuszkovicz, *J. Amer. Chem. Soc.* **76**, 2029 (1954).
[293] E. P. Oliveto, R. Rausser, L. Weber, E. Shapiro, D. Gould and E. B. Hershberg, *J. Amer. Chem. Soc.* **78**, 1736 (1956).
[294] E. M. Chamberlin and J. M. Chemerda, *J. Amer. Chem. Soc.* **77**, 1221 (1955).
[295] H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, *J. Amer. Chem. Soc.* **77**, 4781 (1955).
[296] R. Joly, G. Nominé and D. Bertin, *Bull. Soc. Chim.* 1459 (1956).
[297] Huang-Minlon and R. H. Pettebone, *J. Amer. Chem. Soc.* **74**, 1562 (1952).
[298] D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Amer. Chem. Soc.* **78**, 2912 (1956).
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[300] N. L. Wendler, Huang-Minlon and M. Tishler, *J. Amer. Chem. Soc.* **73**, 3818 (1951).
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[302] A. Stoll, A. von Wartburg and J. Renz, *Helv. Chim. Acta* **36**, 1531 (1953).
[303] W. F. McGuckin and E. C. Kendall, *J. Amer. Chem. Soc.* **74**, 5811 (1952).
[304] H. Reich and R. W. Collins, *J. Amer. Chem. Soc.* **73**, 1374 (1951).
[305] R. E. Jones and S. A. Robinson, *J. Org. Chem.* **21**, 586 (1956).
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[307] E. B. Hershberg, *J. Org. Chem.* **13**, 542 (1948).
[308] D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Amer. Chem. Soc.* **79**, 452 (1957).
[309] E. P. Oliveto, H. L. Herzog, L. Weber, M. E. Tully and E. B. Hershberg, *J. Org. Chem.* **21**, 795 (1956).
[310] L. Velluz, J. Warnant, G. Nominé, R. Joly and A. Petit, *Bull. Soc. Chim.* 906 (1953).
[311] V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.* **70**, 882 (1948).
[312] R. Joly and G. Nominé, *Bull. Soc. Chim.* 1381 (1956).

of saturated, as against α-β-unsaturated ketone groups. A number of examples, utilising exchange with acetone cyanohydrin, have been reported.[313] Reversal to the ketone occurs with bases, but cyanohydrins are reasonably stable to acidic conditions, such as when cyanohydrin formation with a saturated ketone group is followed by ketalisation of an α-β unsaturated ketone, though in such a case it is advisable to add some acetone cyanohydrin in the latter reaction, to minimise reversal and dehydration of the steroid cyanohydrin.[314]

E. SELECTIVE REACTIONS OF HYDROXYL GROUPS

I. *Selective oxidation*

(a) *Chromic acid*, NBS, NBA *and Oppenauer oxidations.* (Table 13.) A definite order in the oxidisability of steroid hydroxyl groups, depending on their configuration and position, was recognised in the early work on the structure of the bile acids.[315,316] This order has since been put on a firmer basis by the crystallisation of modern views on conformational analysis.[149,317,318]

Regarding oxidation with hexavalent chromium; the rate-determining step generally attack on the hydrogen atom on the same carbon as the hydroxyl group, the conformational factor will nearly always determine the order of oxidation among several hydroxyl groups. Oxidation with reagents such as N-bromosuccinimide or N-bromoacetamide[319] is less clear out from the mechanistic viewpoint; it being uncertain whether this proceeds through formation of the steroid alcohol hypohalite, and if so whether the rate-determining step is formation of the hypohalite or abstraction of the α-hydrogen atom.[320] On the one hand, examples are known in which oxidation with NBS appears to follow the same order as for chromic acid.[316,321,322] With the more powerful NBA reagent, however (whose action is enhanced by the presence of *tert.* butyl alcohol[322]) selectivity seems to be governed more by accessibility of the hydroxyl groups; this decidedly is the case with Oppenauer oxidation.

Primary alcohols can in most cases be left unaffected during oxidation of other secondary alcohol groups, both with chromic acid[17,245,323,324] and with hypohalite reagents.[111,325–329]

Oxidation with *tert.* butyl hypochlorite,[239,240,330–332] N-chlorosuccinimide[332] or

[313] A. Ercoli and P. de Ruggieri, *J. Amer. Chem. Soc.* **75**, 650 (1953).
[314] G. Stork and H. J. E. Loewenthal, unpublished results.
[315] L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold, New York (1949).
[316] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.* **71**, 3935 (1949).
[317] J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **38**, 1529 (1955).
[318] W. Klyne, *Progress in Stereochemistry* Vol. I. Butterworths, London (1954).
[319] H. Reich and T. Reichstein, *Helv. Chim. Acta* **26**, 562 (1943).
[320] C. A. Grob and H. J. Schmid, *Helv. Chim. Acta* **36**, 1763 (1953).
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[323] S. Bernstein and R. Lenhard, *J. Amer. Chem. Soc.* **77**, 2331 (1955).
[324] A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *J. Amer. Chem. Soc.* **76**, 6210 (1954).
[325] M. Ehrenstein, G. W. Barber and M. W. Gordon, *J. Org. Chem.* **16**, 349 (1951).
[326] M. Ehrenstein and M. Duennenberger, *J. Org. Chem.* **21**, 774 (1956).
[327] M. Ehrenstein and M. Duennenberger, *J. Org. Chem.* **21**, 783 (1956).
[328] K. Florey and M. Ehrenstein, *J. Org. Chem.* **19**, 1174 (1954).
[329] R. E. Jones and F. W. Kocher, *J. Amer. Chem. Soc.* **76**, 3682 (1954).
[330] J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, *J. Amer. Chem. Soc.* **75**, 3500 (1953).
[331] G. S. Fonken, J. L. Thompson and R. H. Levin, *J. Amer. Chem. Soc.* **77**, 172 (1955).
[332] A. R. Hanze, G. S. Fonken, A. V. McIntosch, A. M. Searcy and R. H. Levin, *J. Amer. Chem. Soc.* **76**, 3179 (1954).

hypochlorous acid[332] appears to be specific to the 3α- or 3β-hydroxyl group, giving the α-chloro ketone; an α-bromo ketone is formed when oxidation with NBA is allowed to proceed in the presence of hydrobromic acid.[332]

A general picture of the order of oxidation by these reagents is provided by the following rules arising out of more systematic work:

TABLE 12

Reagent	Type of compound	Order of oxidation of OH groups	Ref.
CrO_4^{--}/OAc^-	Bile acids	$7\alpha > 12\alpha$	322
$Cr_2O_7^{--}/H^+$	A/B-*trans*-steroids	$11\beta > 11\alpha > 3\beta$	333
NBS/acetone/H_2O	Bile acids,	$7\alpha > 12\alpha$	322
NBS/acetone/H_2O	Cholestane derivatives	$6\beta > 3\beta$	321
NBS/acetone/H_2O	Cholestane derivatives	$7\alpha > 3\beta$	322
NBA/acetone	A/B-*trans*-steroids	$11\beta > 3\beta > 11\alpha$	333, 334
NBA/acetone	A/B-*cis*-steroids	$3\alpha + 17\beta > 11\alpha$	162
NBA/acetone	A/B-*cis*-steroids	$3\alpha > 12\alpha > 12\beta > 17\beta$	319
NBA/acetone	A/B-*cis*-steroids	$11\beta > 11\alpha$	332
TBH	A/B-*cis*-steroids	$3\alpha > 11\alpha + 11\beta$	240, 331, 332

(b) *Oxidation by other methods:* (i) *Manganese dioxide oxidation.* This reagent oxidises selectively allylic as against saturated alcohol groups.[350] It has been used in particular for the synthesis of testosterone and its analogues, through selective oxidation of a suitable androst-4-ene 3:17-diol[51,143,350–354] and applies equally well to oxidation of 4-ene 3-ols in the presence of saturated hydroxyl groups at other positions.[119,252,355,356]

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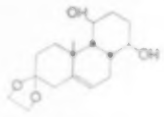
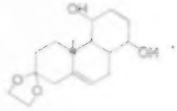
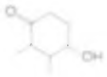
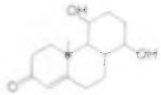
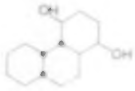
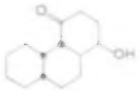
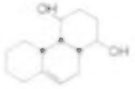
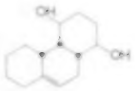
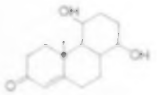
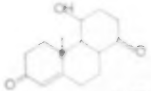
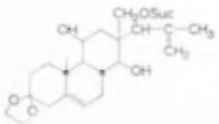
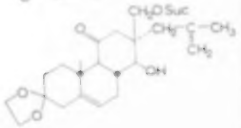
VOL. 6 1959

TABLE 13. EXAMPLES

Compound	Method	Product	Ref.
Androstane derivatives			
5β-H, 3α-acetoxy, 11β:17α-diol	Oppenauer	17-one	335
4-ene, 17-one, 3β:6β-diol	Oppenauer	4-ene, 3:6:17-trione	336
4-ene, 17-one, 3β:6β-diol	CrO_3	4-ene, 3β-ol, 6:17-dione	336
5β-H, 17-carbomethoxy, 3β:1β-diol	NBA, *tert.* BuOH/Py, H_2O	3-one	337
5β-H, 3α:11α:17β-triol	NBA	3:17-dione	162, 163
3β:5α:17β-triol	CrO_3	17-one	338
4-ene, 3β:16α:17β-triol	Oppenauer	4-ene, 3:16-dione	242
4-ene, 17α-hydroxymethyl-ethinyl, 3β:17β-diol	Oppenauer	4-ene 3-one	339
Pregnane derivatives			
5-ene, 20-ethylenedioxy, 3β:16α-diol	Oppenauer	4-ene 3-one	249
5-ene, 3:20-bisethylenedioxy, 11α:21-diol	CrO_3/Py	11-one	323
(*allo*) 16:17α-epoxy, 20-one, 3β:11α-diol	Oppenauer	3-one	340
17(20)-ene, 20-cyano, 11-one, 3α:21-diol	NBA, MeOH/Py	3-one	329
20-one, 3α:11α:17α-triol	NBA, acetone/H_2O	3-one	341, 342
20-one, 3α:11α:17α-triol	TBH	4-chloro 3-one	240
(*allo*) 20-one, 3β:12β:17α-triol	NBA, Py/H_2O	3-one	343
(*allo*) 12-one, 3β:17α:20-triol	NBA, *tert.* BuOH/H_2O	3-one	241
(19-*nor*), 4-ene, 3:20-dione, 11β:17α:21-triol	CrO_3	11-one	324
4-ene, 6α-Me, 3:20-dione, 11β:17α:21-triol	NBA, Py	11-one	111
21-acetoxy, 20-one, 3α:12α-17α-triol	NBA, *tert.* BuOH/Py/H_2O	3-one	341
1:4-diene, 6α-Me, 3:20-dione, 11β:17α:21-triol	NBA/Py	11-one	111
5-ene, 3:20-bisethylenedioxy, 11α:17α:21-triol	CrO_3/Py	11-one	245
3α:11β:17α:20:21-pentol 20:21-acetonide	Oppenauer	3-one	344
Cholestane derivatives			
5-ene, 3β:7β-diol	Oppenauer	4-ene 3-one	345
3β:7α-diol	NBS	7-one	322
3β:5α:6β-triol	NBS	6-one	321

TABLE 13. (*contd.*)

Compound	Method	Product	Ref.
Other compounds			
*Isoallo*spirostane 3β:11β-diol	Oppenauer	3-one	333
Methyl cholate 7-acetate	K_2CrO_4, HOAc	12-one	322
Methyl cholate and -desoxy-cholate	Oppenauer	3-one	346
Synthetic intermediates			
	Oppenauer		347
	CrO_3/Py		347
	NBA		347
	CrO_3		148
	CrO_3		148
	Oppenauer		148
	CrO_3/Py		348
	1 mole CrO_3/Py		349

An interesting case is provided by 16-methylene androst-4-ene 3:17-diol;[51] here the allylic 3-hydroxy group is oxidised in preference to the "exocyclically" allylic 17-hydroxy group.

4-Ene 3:6-diols are oxidised to 6-hydroxy 4-ene 3-ketones.[85,350,357] Under vigorous conditions (in benzene solution at 72°) oxidation may proceed further in certain cases and give 4:6-diene 3-ketones from both 4-ene 3-ketones and 5-ene 3β-alcohols,[358] while cholesteryl acetate is reported to give a small amount of the 7-keto compound.[359]

The activity of manganese dioxide in this type of oxidation depends greatly on its method of preparation; the most suitable reagent being that made by precipitation from alkaline solution.[360]

(ii) *Catalytic oxidation.* Platinum oxide and oxygen, usually in ethyl acetate solution, can oxidise specifically highly accessible secondary alcohol groups (3α and 3β) in a number of hydroxy steroids,[361] but this has been reported to fail with cholesterol. This method has been employed with success in the field of highly hydroxylated compounds derived from cardiac aglycones.[362]

II. *Various selective reactions of hydroxyl groups*

11β- or 9βH-11α-[14]Hydroxyl groups are dehydrated under conditions which do not affect tertiary 17α-hydroxyl groups.[229,233,363] The tertiary 5α-[364] and 5β-hydroxy[327,365] group is left unchanged under conditions used for dehydration of the 14β-hydroxy group (phosphorus oxychloride, pyridine).

In certain cases allylic[366] or homoallylic[367] as against saturated hydroxyl groups can be converted selectively into the corresponding chlorides.

In the 17α:21-diol-20-one cortical side chain the 17α-hydroxyl group can be removed by catalytic hydrogenolysis after formation of a 21-dibenzyl acetal.[255]

F. MODIFICATION OF HYDROXYL GROUPS

I. *Selective ester formation and hydrolysis*

(a) *General.* Formation of an ester, usually an acetate, is the most useful method of protecting a hydroxyl group against reactions proceeding under acidic conditions, such as oxidation. Selective formation of esters and their selective hydrolysis are governed by both conformational and positional factors. Acylating groups larger than acetyl, such as benzoyl or succinoyl, are usually chosen for the greater selectivity they confer both in acylation and hydrolysis.

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[361] R. P. A. Sneeden and R. B. Turner, *J. Amer. Chem. Soc.* **77**, 190 (1955).
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[366] B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, *J. Biol. Chem.* **173**, 271 (1948).
[367] J. Broome, B. R. Brown and G. H. R. Summers, *J. Chem. Soc.* 2071 (1957).

Formates have been used because of their very facile hydrolysis under basic conditions[368,369] and because they can be formed with very hindered hydroxyl groups (e.g. at C_{11}); the same applies to trifluoroacetates.[370] They are reported to be stable to acidic conditions, to metal hydride reduction in non-hydroxylic solvents[371] and to potassium acetate in acetone.[372]

Carbonate ester formation (usually from ethyl chloroformate and the alcohol in pyridine) is reported to be highly specific to equatorial alcohol groups.[373] Carbonates are stable to acidic conditions and to the action of peracids;[201] and are of additional interest in that they are easily eliminated by pyrolysis to give olefins.[374]

Regarding *p*-toluene sulphonates and methanesulphonates; these are reasonably stable to mild basic conditions, such as during metal hydride reduction.[4,375–377] Tosylation is less affected by steric factors than acetylation[378,379] and is more selective than mesylation.[380] In all cases, a primary alcohol group will be acylated before a secondary hydroxyl group. 20-Keto 21-ols are not tosylated with *p*-toluene sulphonyl chloride and pyridine but give pyridinium salts.[381]

(b) 11-*Hydroxy groups*. 11α-Hydroxy groups are reported to be acetylated fairly easily,[254,258] 11β-hydroxyl groups only after prolonged reaction; e.g. with acetic anhydride/pyridine at 100° for 24 hours,[382] with acetic anhydride and *p*-toluenesulphonic acid,[211,353] with acetyl chloride[383] or with *iso*propenyl acetate.[384] When very vigorous conditions are used, enol acetylation of a 20-ketone group may be unavoidable but can be reversed on working up under mildly alkaline conditions.[353] Less information is available on the hydrolysis of 11β-acetates.[211] The resistance of 11-hydroxy groups to acetylation disappears in a 12:13-ene 11-ol.[385]

(c) *Tertiary hydroxyl groups*. 17α-Hydroxyl groups can be acetylated under reasonably vigorous conditions[386,387] as can 5α- (but not 5β) hydroxyl groups.[11] Such tertiary ester groups are fairly stable to alkaline conditions but their hydrolysis presents no special problems as in the case of 11β-esters.

(d) *Miscellaneous*. Acetylation can be carried out using phenyl acetate and sodium hydride to avoid mixed anhydride formation with a carboxyl group,[388] or by ester exchange with ethyl acetate in the presence of an acid catalyst[389] to prevent

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[374] G. L. O'Connor and H. R. Nace, *J. Amer. Chem. Soc.* **74**, 5454 (1952).
[375] M. N. Huffman, M. H. Lott and A. Tillotson, *J. Biol. Chem.* **218**, 565 (1956).
[376] J. H. Looker and D. N. Thatcher, *J. Org. Chem.* **19**, 784 (1954).
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[378] F. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **75**, 2273 (1953).
[379] R. Hirschmann, C. S. Snoddy and N. L. Wendler, *J. Amer. Chem. Soc.* **74**, 2693 (1952).
[380] A. Corbellini and G. Nathansohn, *Gazz.* **86**, 1240 (1956).
[381] W. J. Leanza, J. P. Conbere, E. F. Rogers and K. Pfister, *J. Amer. Chem. Soc.* **76**, 1691 (1954).
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[385] H. L. Herzog, C. C. Joyner, M. J. Gentles, M. T. Hughes, E. P. Oliveto, E. B. Hershberg and D. H. R. Barton, *J. Org. Chem.* **22**, 1413 (1957).
[386] E. Batres, R. Gomez, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.* **21**, 240 (1956).
[387] R. B. Turner, *J. Amer. Chem. Soc.* **75**, 3489 (1953).
[388] R. Pappo, B. M. Bloom and W. S. Johnson, *J. Amer. Chem. Soc.* **78**, 6347 (1956).
[389] W. S. Johnson, E. R. Rogier and J. Ackerman, *J. Amer. Chem. Soc.* **78**, 6322 (1956).

acetylation of a phenolic hydroxy group, even though generally phenols are acylated under the usual conditions with greater difficulty than secondary alcohols.[390,391]

While esters of equatorial 3-alcohols are hydrolysed more easily than their axial epimers, the reverse may occur in the presence of a hydroxyl group at C_5.[392]

TABLE 14. SELECTIVE ESTER FORMATION

A/B-*trans*-steroids		A/B-*cis*-steroids		Δ^5-steroids		Δ^4-3-keto-steroids	
Order	Ref.	Order	Ref.	Order	Ref.	Order	Ref.
Acetates							
$3\beta > 1\alpha$	393	$3\beta > 1\beta$	395	$21^a > 3\beta$	396	$21^a > 6\beta$	259
$3\alpha > 1\alpha$	393	$3\alpha > 12\alpha$	185			$21^a > 11\alpha + 17\alpha^c$	378
$3\beta > 7\alpha$	394	$3\alpha + 7\alpha > 12\alpha$	322			$21^b > 11\alpha$	397
$3\beta > (9\beta H)11\alpha$	14	$3\alpha + 17\beta > 11\beta$	162			$21^b > 16\alpha$	398
$3\beta > 11\beta$	382	$21^c > 20\alpha$	169				
$20^d > 3\alpha$	399						
$20^d > 3\beta > 1\alpha$	399						
Carbonates		$3\alpha > 12\alpha$	400				
		$3\alpha > 12\alpha + 17\alpha^c$	341				
		$3\alpha > 7\alpha + 12\alpha$	316				
			322				
Formates		$3\alpha > 17\alpha^c + 11\beta$	186				
		$3\alpha > 12\beta^f$	279				
Succinates							
$3\beta > 12\alpha$ or 12β	379	$3\alpha > 12\alpha$	206				
			401				
$3\beta > 11\beta$	424	$3\alpha > 7\alpha$	322				
			402				
		$3\alpha > 12\beta$	403				
Benzoates				$3\beta > 7\alpha^f$	404		
p-*Toluenesulphonates*							
$3\beta > 6\beta^g$	4						
	377						
	380						
Methanesulphonates							
$16\alpha > 11\beta + 17\alpha^c$	227						

[a] 17α-hydroxy 20-keto 21-alcohol. [b] 20-keto 21-alcohol. [c] tertiary alcohol.
[d] 20-hydroxy 21-nor steroid. [e] Primary alcohol. [f] Acetylation was not selective in this case.
[g] Mesylation was not selective in this case.

[390] N. Borsel, *J. Amer. Chem. Soc.* **74,** 251 (1952).
[391] M. N. Huffman and M. H. Lott, *J. Biol. Chem.* **172,** 325 (1948).
[392] H. B. Henbest and B. J. Lovell, *Chem. & Ind.* 278 (1956).
[393] P. Striebel and C. Tamm, *Helv. Chim. Acta* **37,** 1094 (1954).
[394] D. H. R. Barton and G. F. Laws, *J. Chem. Soc.* 52 (1954).
[395] W. Schlegel and C. Tamm, *Helv. Chim. Acta* **40,** 160 (1957).
[396] K. Florey and M. Ehrenstein, *J. Org. Chem.* **19,** 1331 (1954).
[397] F. Reber, A. Lardon and T. Reichstein, *Helv. Chim. Acta* **37,** 45 (1954).
[398] E. Vischer, J. Schmidlin and A. Wettstein, *Helv. Chim. Acta* **37,** 321 (1954).
[399] F. Sallmann and C. Tamm, *Helv. Chim. Acta* **39,** 1340 (1956).
[399a] E. J. Salmi, *Ber.* **71,** 1803 (1938).
[400] R. Casanova, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 2983 (1953).
[401] E. B. Hershberg, H. L. Herzog, S. B. Coan, L. Weber and M. Jevnik, *J. Amer. Chem. Soc.* **74,** 2585 (1952).
[402] H. P. Sigg and T. Reichstein, *Helv. Chim. Acta* **39,** 1507 (1956).
[403] E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.* **177,** 951 (1949).
[404] H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 1792 (1948).

TABLE 15. SELECTIVE ESTER HYDROLYSIS

A/B-*trans*-steroids			A/B-*cis*-steroids			Δ^5-steroids			Δ^4-3-keto-steroids		
Order	Method	Ref.	Order	Method	Ref.	Order	Method	Ref.	Order	Method	Ref
Acetates											
$3\beta > 1\alpha$	F	393	$3\beta > 6\beta$	C	409	$3\beta > 1\beta$	F	411	$21^a > 11\alpha$	F	342
$3\beta > 6\beta$	C	405, 406	$3\beta > 11\alpha$	F	397	$3\beta > 17\beta$	C	412	$21^b > 11\alpha$	A	397
$3\beta > 11\alpha$	A	334	$3\alpha > 12\alpha$	B	341	$3\beta > 17\beta$	B	413	$21^b > 19^e$	A	416, 417
$3\beta > 17\beta$	B	407	$3\alpha > 17\alpha^c + 11\beta$	F	211	$3\beta > 16\beta$	A	414			
$3\beta > 20\beta + 16\alpha$		171	$3\alpha > 20\alpha$	C	410	$3\beta > 16\alpha + 20\alpha$	A	73			
$3\beta + 20^d > 1\alpha$	F	399	$3\alpha + 12\alpha > 7\alpha$		277	$19^e > 3\beta$	B	326			
$21^b + 3\beta > 11\alpha$	C	408	$17\alpha^c > 11\beta$	B	211	$21^a > 3\beta$	D	396			
			$21^b + 3\alpha > 11\alpha$	C	408	$21^d > 3\beta$	A	415			
Other esters											
3β-benz.											
$>7\beta$-benz.	D	418	3α-form.			3β-form.					
			$>21^b$-acet.	F	419	$>16\alpha$-acet.	A	74			
			21^b-form.			3β-acet.					
			$>3\alpha$-acet.	A	410	$>20\alpha$-benz.	E	420			
						3β-tos. $>16\beta$-tos.	G	421			

Conditions used for hydrolysis are indicated as follows:

HCO_3^-/MeOH ⟶ A OMe^-/MeOH ⟶ D

CO_3^{--}/MeOH ⟶ B OH^-/dioxan ⟶ E H^+/acetone ⟶ G

OH^-/ROH ⟶ C H^+/MeOH ⟶ F

[a] 17α-hydroxy 20-keto 21-ester [b] 20-keto 21-ester [c] tertiary ester [d] 21-nor 20-ester [e] primary ester

[405] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 1790 (1952).
[406] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 3361 (1952).
[407] D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.* 245 (1953).
[408] F. Sondheimer, G. Rosenkranz, O. Mancera and C. Djerassi, *J. Amer. Chem. Soc.* **75**, 2601 (1953).
[409] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 2876 (1955).
[410] L. H. Sarett, *J. Amer. Chem. Soc.* **71**, 1165 (1949).
[411] C. Sannié and H. Lapin, *Bull. Soc. Chim.* 1237 (1957).
[412] P. L. Julian, E. W. Meyer and H. C. Printy, *J. Amer. Chem. Soc.* **70**, 3872 (1948).
[413] P. Wieland and K. Miescher, *Helv. Chim. Acta* **32**, 1768 (1949).
[414] Y. Sato, H. G. Latham and E. Mosettig, *J. Org. Chem.* **22**, 1496 (1957).
[415] F. Giral, *J. Amer. Chem. Soc.* **72**, 1913 (1950).
[416] G. W. Barber and M. Ehrenstein, *J. Org. Chem.* **19**, 1758 (1954).
[417] G. W. Barber and M. Ehrenstein, *J. Amer. Chem. Soc.* **76**, 2026 (1954).
[418] H. Heymann and L. F. Fieser, *Helv. Chim. Acta* **35**, 631 (1952).
[419] J. Warnant, *Bull. Soc. Chim.* 1456 (1956).
[420] R. B. Turner and D. M. Voitle, *J. Amer. Chem. Soc.* **73**, 2283 (1951).
[421] M. N. Huffman, M. H. Lott and A. Tillotson, *J. Biol. Chem.* **222**, 447 (1956).

In view of the great number of examples in the literature both of selective acylation and of selective hydrolysis of esters, results have been given in a shortened tabular form. (Tables 14 and 15.)

II. *Ethers*

(a) *Tetrahydropyranyl ethers.* Formation of tetrahydropyranyl ("THP") ethers, by reaction of a primary or secondary alcohol group with dihydropyran in a solvent such as chloroform or methylene chloride in the presence of a trace of acid, is an excellent method for protection of the hydroxyl group under basic reaction conditions.[422,423] They are stable to conditions of oxidative cleavage[424,425] or epoxidation[426] with alkaline hydrogen peroxide, and will protect the hydroxyl group during Dieckmann cyclisation,[425] reaction with Grignard reagents,[189] lithium alkyls[422a] and reduction with metal hydrides.[194,423] They are stable at high temperatures (pyrolitic elimination of ester groups,[427]) and reasonably stable in acetic acid solution as for example during chromic acid oxidation[140] of another hydroxyl group. They have been used in the preparation of 7-hydroxy 4-ene-3-keto-steroids: Oppenauer oxidation of a free 5-ene-3:7-diol gave only a low yield of the desired compound, while carrying out the reaction on the 7-THP ether 3-acetate was successful.[428]

A disadvantage of using dihydropyran to protect secondary alcohol groups lies in the formation of an additional asymmetric centre, leading in most cases to a mixture of stereoisomeric ethers, but this does not usually detract from the value of this method.

(b) *Triphenylmethyl ethers.* The conditions of stability of these ethers are similar to those of tetrahydropyranyl ethers.[325,365,429] Their formation is specific to primary[325,365] or easily accessible secondary[189] hydroxyl groups, and like tetrahydropyranyl ethers they are easily cleaved by dilute mineral acids.

[422] W. G. Dauben and H. L. Bradlow, *J. Amer. Chem. Soc.* **74**, 559 (1952).
[422a] C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 1190 (1951).
[423] A. C. Ott, M. F. Murray and R. L. Pederson, *J. Amer. Chem. Soc.* **74**, 1239 (1952).
[424] W. S. Johnson and D. S. Allen, *J. Amer. Chem. Soc.* **79**, 1261 (1957).
[425] W. S. Johnson, B. Bannister and R. Pappo, *J. Amer. Chem. Soc.* **78**, 6331 (1956).
[426] H. J. Ringold, E. Batres, O. Mancera and G. Rosenkranz, *J. Org. Chem.* **21**, 1432 (1956).
[427] R. Hirschmann, C. S. Snoddy, C. F. Hiskey and N. L. Wendler, *J. Amer. Chem. Soc.* **76**, 4013 (1954).
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VOL. 6 1959

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ANHYDROBIISATIC ACID

6:12-OXA-5:6:11:12-TETRAHYDROPHENHOMAZINE-6:12-DICARBOXYLIC ACID

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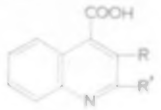
Abstract—Anhydrobiisatic acid (IVa), a new type of compound containing the phenhomazine ring system, has been obtained by self-condensation of isatic acid—(*o*-aminophenyl)glyoxylic acid—. The structure of this acid has been established and derivatives have been prepared. N:N'-Dimethylanhydrobiisatic acid (IVc) has been resolved into optically active components.

IT has long been known that isatin will dissolve in aqueous alkalies to give salts of isatic acid.[1,2,3] These salts, in aqueous or aqueous-alcoholic solution, can condense with ketones (Pfitzinger reaction)[4] to furnish substituted cinchoninic acids (I).



I

Condensation of isatin with various diketones, were found to give the best yields of substituted cinchoninic acids by heating the dry potassium salt of isatic acid with the diketone in the absence of solvent.[5] The yields were usually reproducible, but in some cases, when repeating the experiments, the reaction either failed or gave only traces of the expected product. As the conditions were identical, the only reason for such failure could lie in the composition of the derivative prepared from isatin and potassium hydroxide.

The reaction between isatin and aqueous potassium hydroxide has therefore been investigated. According to experimental conditions, two different potassium salts can be obtained; a *yellow* one, which is the major product when isatin is treated with one equivalent of 20% aqueous potassium hydroxide at temperatures below 40°, and a *colourless* salt, resulting from the reaction of isatin with excess of concentrated (40%) aqueous potassium hydroxide under reflux. By heating the yellow salt in aqueous alkali, it is converted to the colourless compound, whereas the latter is not changed under similar conditions. Two series of salts can be derived from these compounds; the yellow salt gives an orange lead and yellow barium and silver salts; the colourless potassium salt, on the other hand, affords colourless salts with these metals. The iron, copper and nickel salts, in both series, are coloured, with slight differences between the corresponding members of each series.

It is the yellow potassium salt which condenses with diketones to give substituted cinchoninic acids; the colourless salt does not react. By acidifying an aqueous

* Taken, in part, from the Ph.D. dissertation of Lj. Lorenc.

[1] O. L. Erdmann, *J. Prakt. Chem.* **24**, 1 (1841); *Ann. Chim. Phys.* **3**, 355 (1841).

[2] A. Laurent, *Ann. Chim. Phys.* **3**, 371 (1841).

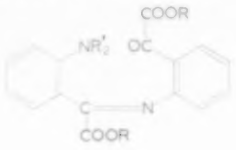
[3] G. Heller, *Ber. Dtsch. Chem. Ges.* **40**, 1291 (1907).

[4] For references, see W. C. Sumpter, *Chem. Rev.* **34**, 393–434 (1944).

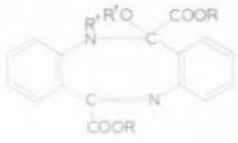
[5] Gj. Stefanović, M. Pavičić-Woss, Lj. Lorenc and M. Lj. Mihailović, *Tetrahedron*, **6**, 97 (1959).

solution containing the yellow salt, isatin is immediately formed, whereas from the colourless salt, a colourless acid, m.p. 176°, is obtained, which can be isolated and purified. In aqueous solution this acid is slowly converted to isatin, the conversion being accelerated by heating or addition of acid. However, it is stable in the solid state when perfectly pure. The same acid is obtained by decomposing the colourless lead salt with hydrogen sulphide. On the other hand, the orange lead salt, when treated in the same way, gives isatin as the sole product.

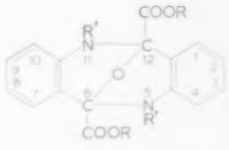
From analytical data and from the chemical behaviour just mentioned, it can be concluded that the yellow potassium salt and related salts are salts of isatic acid, whereas the colourless salts and the corresponding acid, m.p. 176°, are condensation products of isatic acid, formed from two molecules of the acid with elimination of water. Three structures* can be envisaged for the new *anhydrobiisatic acid* (II, III or IV), in agreement with the molecular formula $C_{16}H_{12}O_5N_2$.



II



III



IV

(a) R = R′ = H (b) R = CH_3, R′ = H (c) R = H, R′ = CH_3
(d) R = R′ = CH_3

It appears from the literature that the compounds described as salts of isatic acid are either mixtures of both salts or salts of one or the other series. Erdmann[1] reported a colourless potassium salt and colourless barium and lead salts, whereas the silver salt is described either as colourless or yellow. In contrast, Laurent[2] obtained a pale yellow potassium salt and yellow silver and lead salts. The sodium, silver and lead salts prepared by Heller[3] were all yellow. Attempts to obtain isatic acid from these salts failed; isatin was always the final product.[1,2,3,6] Only in one case, namely by treating the colourless lead salt with hydrogen sulphide, was Erdmann[1] able to isolate a colourless solid which, in aqueous solution, underwent facile conversion to isatin. This product was regarded by Erdmann as isatic acid. However, from the present work, it appears that this compound is in fact anhydrobiisatic acid rather than isatic acid. Moreover, it is now well known that isatic acid and its N-alkyl or N-aryl derivatives cannot be isolated, in contrast to N-acylated isatic acids, which have been prepared in several instances.[7]

* Structures corresponding to II[8] and III[9] have been ascribed (without any proof) to anhydro*bis*(*o*-aminobenzaldehyde), a self-condensation product of *o*-aminobenzaldehyde. Similar constitutions have been also proposed for higher condensation products of *o*-aminobenzaldehyde.[10]

[6] L. Claisen and J. Shadwell, *Ber. Dtsch. Chem. Ges.* **12**, 350 (1879); G. Heller, *Ibid.* **37**, 938 (footnote 2) (1904); E. Deussen, G. Heller and O. Nötzel, *Ibid.* **40**, 1300 (1907).

[7] W. Suida, *Ber. Dtsch. Chem. Ges.* **11**, 584 (1878); C. Schotten, *Ibid.* **24**, 772 (1891); M. T. Bogert and F. P. Nabenhauer, *J. Amer. Chem. Soc.* **46**, 1702 (1924); J. A. Aeschlimann, *J. Chem. Soc.* 2902 (1926); R. K. Callow and E. Hope, *Ibid.* 1191 (1929); W. Steinkopf and H. Wilhelm, *Liebigs Ann.* **546**, 211 (1942); R. Johnstone and J. R. Price, *Aust. J. Chem.* **7**, 209 (1954); T. Sato and M. Ohto, *Bull. Chem. Soc. Japan* **28**, 480 (1955).

[8] P. Friedländer and R. Henriques, *Ber. Dtsch. Chem. Ges.* **15**, 2105 (1882); P. Friedländer and C. F. Göhring, *Ibid.* **17**, 456 (1884).

[9] P. Friedländer, *C. R. Acad. Sci., Paris* **136**, 370 (1902).

[10] E. Bamberger and E. Demuth, *Ber. Dtsch. Chem. Ges.* **36**, 835 (1903); E. Bamberger, *Ibid.* **36**, 2046 (1903); *Ibid.* **60B**, 314 (1927); F. Seidel, *Ibid.* **59**, 1894 (1926).

Anhydrobiisatic acid is quite a strong acid, pK_1 (water) 2·88. It does not undergo reactions characteristic for the carbonyl, hydroxyl and primary amino groups. Hydrogenation in the presence of platinum, platinic oxide, palladium or Raney nickel was unsuccessful. Its colourless potassium salt is not attacked by sodium borohydride in aqueous solution, even after prolonged heating. By treating anhydrobiisatic acid with diazomethane in anhydrous ether, a compound having the molecular formula $C_{18}H_{16}O_5N_2$ (analysis and molecular weight determination) was isolated. It, therefore contains two additional CH_2 groups.* This compound, stable in contrast to the free acid, is insoluble in sodium bicarbonate solution but can easily be saponified to the starting acid. These properties (and the saponification value) correspond to the dimethyl ester of anhydrobiisatic acid (although it is insoluble in ether and melts higher than the acid from which it is derived). It is also resistant to catalytic hydro-genation and does not give derivatives with specific reagents for the carbonyl, primary amino hydroxyl groups. The behaviour of anhydrobiisatic acid and of its dimethyl ester, and the fact that all compounds of this series (with the exception of the iron, copper and nickel salts) are colourless, make structures II and III improbable.†

Conclusive evidence for structure IV is obtained from methylation experiments of anhydrobiisatic acid. When the silver salt of anhydrobiisatic acid is treated with methyl iodide in anhydrous ether, a new acid is formed, m.p. 154°, isomeric with the dimethyl ester of anhydrobiisatic acid. The same acid, but crystallizing with two molecules of water (m.p. 118°), is obtained from the potassium salt of anhydrobiisatic acid and dimethyl sulphate, in aqueous solution.‡ Examples reported in the literature,[12] indicate that methylation of salts of amino acids with dimethyl sulphate and methyl iodide, in aqueous or anhydrous media, usually give N-methylated amino acids and not N-unsubstituted esters. The new acid should, accordingly, contain the two additional methyl groups on nitrogen (or on nitrogen and on hydroxyl oxygen, in the case of structure IIIc) and, on hydrolysis, would be expected either to give a mixture of isatin and N-methylisatin or other products (structures IIc and IIIc), or solely N-methylisatin (structure IVc).

The new dimethylated acid has properties similar to those of anhydrobiisatic acid. It is a rather strong acid, pK_1 (ethanol) 3·92, stable only in the solid form and when completely pure. In aqueous solution, upon heating or upon addition of mineral

* In case of structure III, the hydroxyl group, being activated by the presence of other functional groups, would possibly undergo methylation (to a certain extent) with diazomethane,[11] although the neutralizing effect of anhydrous ether should not be disregarded.[12]

† It may be assumed that a *cis* configuration of structure II would be sterically hindered, thus preventing the usual reactions of the carbonyl and amino groups. Examination of models, however, suggests that under drastic alkaline conditions, such as are used for obtaining the potassium salt of anhydrobiisatic acid, *cis*-II should undergo facile condensation between the carbonyl and amino groups, with elimination of water. For this reason also, an aldehyde-ammonia structure, such as III, is *a priori* highly improbable. Both structures II and III, moreover, should be attacked by sodium borohydride and catalytically activated hydrogen, in contrast to IV, which has no reducible groups.

‡ The identity of both acids was established by conversion of the anhydrous acid, m.p. 154°, to the hydrated acid, m.p. 118°.

[11] O. T. Schmidt and H. Zeiser, *Ber. Dtsch. Chem. Ges.* **67B**, 2120, 2127 (1934).

[12] H. Meerwein and G. Hinz, *Liebigs Ann.* **484**, 1 (1930).

[13] K. Kraut, *Liebigs Ann.* **180**, 172 (1876); G. Körner and A. Menozzi, *Gazz. Chim. Ital.* **13**, 350 (1883); G. Fortmann, *J. Prakt. Chem.* **55**, 123 (1897); R. Willstätter and W. Kahn, *Ber. Dtsch. Chem. Ges.* **37**, 401 (1904); J. Houben and W. Brassert, *Ibid.* **39**, 3233 (1906); J. Novák, *Ibid.* **45**, 834 (1912); T. Imai, *Z. Physiol. Chem.* **136**, 192 (1924).

acids, it is quickly and quantitatively converted to N-methylisatin.* The fact that one mole of acid gives two moles of N-methylisatin (and no isatin) is compatible only with structure IVc.

N:N′-Dimethylanhydrobiisatic acid (IVc) is converted to its dimethyl ester (IVd) by diazomethane, dimethyl sulphate (in aqueous solution) or methyl iodide (using the silver salt of the acid suspended in anhydrous ether). This diester, like that of anhydrobiisatic acid (IVb), is sparingly soluble in ether (although to a somewhat greater extent than the dimethyl ester IVb) and melts higher than the corresponding acid (m.p. 173°). Upon saponification, it gives the original acid (IVc), in 96% yield. Both the acid (IVc) and its dimethyl ester (IVd) are colourless compounds.

Additional evidence for structure IV was obtained by resolving N:N′-dimethylanhydrobiisatic acid (IVc) into its optically active components. The (+)-acid had a specific rotation of +51·3° and the (−)-antipode −50·6° (in ethanol). As can be seen from Fig. 1, the geometry of the molecule of anhydrobiisatic acid and its derivatives is such as to permit the existence of one pair of optically active enantiomers.†

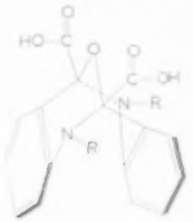


FIG. 1.

The study of the infra-red spectra does not provide much evidence for differentiating between structures II, III and IV, but the spectra are useful for ascertaining the presence of functional groups in the derivatives of anhydrobiisatic acid. Except for the potassium salt of isatic acid, which shows a double band in the 3360–3460 cm^{-1} region (primary amino group), anhydrobiisatic acid and its derivatives (IV) produce only one band, indicating the presence of secondary or tertiary amino groups. A single strong band in the 1130 cm^{-1} region is observed in all compounds of the anhydrobiisatic acid series, which is absent in the spectrum of the potassium salt of isatic acid. This vibration may be due to the presence of an ether linkage.

The ultra-violet spectra are of interest. Considering the potassium salt of isatic acid, it is clear that the ionized carboxyl group cannot participate in the conjugation of the molecule. Its absorption spectrum should, therefore, be similar to those of compounds of the *o*-aminoacetophenone type.[15] This expectation proved to be correct, as can be seen from Table 1. The spectra of the compounds of the anhydrobiisatic acid series are similar to each other but quite different from the spectrum of the potassium salt of isatic acid. Moreover, they resemble the absorption curves of the

* By treating the yellow silver salt of isatic acid with methyl iodide[3] or the corresponding yellow potassium salt with dimethyl sulphate,[3,14] a mixture of isatin and N-methylisatin is obtained, the latter being the major product.

† Structure II cannot give rise to optically active isomers, whereas structure III contains an asymmetric carbon atom and is theoretically resolvable.

[14] P. Friedländer and S. Kielbasinski, *Ber. Dtsch. Chem. Ges.* **44**, 3098 (1911); W. Borsche and W. Jacobs, *Ibid.* **47**, 354 (1914); M. Kohn and A. Ostersetzer, *Mh. Chem.* **34**, 787 (1913); *Ibid.* **37**, 25 (1916).

[15] P. Grammaticakis, *Bull. Soc. Chim. Fr.* 93, 865 (1953).

[16] R. G. Ault, E. L. Hirst and R. A. Morton, *J. Chem. Soc.* 1653 (1935); L. Marchlewski and A. Moroz, *Bull. Soc. Chim. Fr.* **37**, 404 (1925).

[17] W. C. Sumpter, J. L. Williams, P. H. Wilken and B. L. Willoughby, *J. Org. Chem.* **14**, 713 (1949).

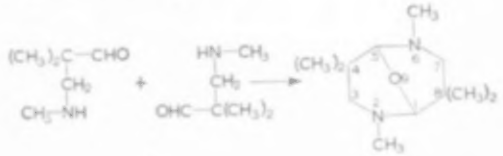
TABLE 1. ULTRA-VIOLET ABSORPTION SPECTRA

Compound	λ_{max} in mμ	(log ε)	λ_{min} in mμ	(log ε)	Solvent
Potassium salt of isatic acid*	229·5	4·25	251	3·74	Water
	264	3·88	290	2·19	
	373	3·64			
o-Aminoacetophenone[15]	228	4·28	248	3·58	Ethanol
	259	3·75	281	2·10	
	365	3·72			
IVa (Potassium salt)	236	4·07	228·2	4·03	Water
	288·5	3·38	270·8	3·20	
IVb	238	4·16	228	4·08	Ethanol
	292	3·56	272	3·36	
IVd	240	4·02 (infl.)	272	3·34	Ethanol
	288	3·43			
(*o*-Aminophenyl)acetic acid (Sodium salt)[18]	234	3·91	260	2·87	Water
	282	3·28			
N-Methyl-*o*-toluidine[19]	242	3·96	267	2·92	Ethanol
	292	3·27			

* Similar spectra have been reported for solutions of isatin in aqueous sodium hydroxide (actually containing the sodium salt of isatic acid).[16] However, Sumpter *et al.*[17] have described a very different spectrum for isatin in a solution buffered at pH 11·6 (which should contain the same anion of isatic acid).

sodium salt of (*o*-aminophenyl)acetic acid[18] and N-methyl-*o*-toluidine[19] (Table 1), suggesting the presence of structure IV, but differ largely from the spectra of compounds of the N-benzalaniline type,[20] possessing the grouping Ar—N=C(R)—Ar, which should be present in the case of structures II or III.

From all the facts, the only possible constitution which can be assigned to anhydrobiisatic acid is the structure of 6:12-*oxa*-5:6:11:12-*tetrahydrophenhomazine*-6:12-*dicarboxylic acid* (IVa; Fig. 1). In one case reported in the literature the substituted 9-oxa-2:6-diazabi*cyclo*(3:3:1)nonane ring system (VI) has been tentatively proposed for the product obtained by self-condensation of 2-dimethyl-3-(methylamino)-1-propionaldehyde (V).[21] In the light of the present work this structure is probable. Compound VI is unstable and, like anhydrobiisatic acid (IVa), is easily converted, by acids, to the starting aminoaldehyde V.



V VI

[15] P. Ramart-Lucas, *Bull. Soc. Chim. Fr.* **1**, 1133 (1934); P. Ramart-Lucas and D. Biquard, *Ibid.* **2**, 1383 (1935).
[16] A. Wohl, *Bull. Soc. Chim. Fr.* **6**, 1312 (1939); P. Grammaticakis, *Ibid.* 134 (1949); P. Ramart-Lucas and J. Klein, *Ibid.* 454 (1949).
[17] A. v. Kiss and G. Auer, *Z. Phys. Chem.* **A 189**, 344 (1941); E. Hertel and M. Schinzel, *Ibid.* **B 48**, 289 (1941); L. N. Ferguson and G. E. K. Branch, *J. Amer. Chem. Soc.* **66**, 1467 (1944); F. W. Holly and A. C Cope, *Ibid.* **66**, 1875 (1944).
[21] C. Mannich and H. Wieder, *Ber. Dtsch. Chem. Ges.* **65B**, 385 (1932); see also C. Mayer, *Bull. Soc. Chim. Fr.* **7**, 481 (1940).

VOL. 6 1959

EXPERIMENTAL

Melting points are not corrected.

The ultra-violet absorption spectra were obtained with a Beckman ultra-violet spectrophotometer, Model DU; and the infra-red absorption spectra with a Perkin-Elmer double-beam infra-red spectrometer, Model 21. Potassium bromide pellets were used for infra-red analysis.

Derivatives of isatic acid [(o-*aminophenyl*)*glyoxylic acid*]

Potassium isatate. 20% Aqueous KOH, containing 0·1 mole of base, was slowly added to 14·7 g (0·1 mole) isatin, the mixture being gently warmed to 40°. The change of colour from dark red-violet to yellow indicated the end of the reaction. The solution was evaporated to dryness under reduced pressure (below 40°) and the yellow *potassium isatate* was recrystallized from ethanol. (Found: K, 19·42; $C_8H_6O_3NK$ requires: K, 19·24%).

Silver isatate. A solution containing 5·1 g (0·025 mole) of potassium isatate in 50 ml water was mixed with 4·7 g silver nitrate dissolved in 50 ml water. The yellow precipitate was filtered and washed with water, and dried. (Found: Ag, 39·52; $C_8H_6O_3NAg$ requires: Ag, 39·66%).

Anhydrobiisatic acid (6:12-*oxa*-5:6:11:12-*tetrahydrophenhomazine*-6:12-*dicarboxylic acid*) *and derivatives*

Potassium anhydrobiisatate. 40% Aqueous KOH (20 ml), was added to 14·7 g (0·1 mole) isatin. The resulting solution was refluxed (30 min) and evaporated (steam-bath). The solid residue, after washing with boiling ethanol (2 × 50 ml), and after recrystallization from ethanol–water, consisted of pure, colourless *potassium anhydrobiisatate* (18·2 g; 93·7%). (Found: N, 7·17; K, 20·42. $C_{16}H_{10}O_5N_2K_2$ requires: N, 7·21; K, 20·13%).

Silver anhydrobiisatate. A solution containing 9·7 g (0·025 mole) potassium anhydrobiisatate in 100 ml water was mixed with 9·4 g silver nitrate dissolved in 100 ml water. The colourless precipitate of the *silver anhydrobiisatate* was washed with water and dried. (Found: Ag, 40·91; $C_{16}H_{10}O_5N_2Ag_2$ requires: Ag, 41·02%).

Anhydrobiisatic acid (IVa). A solution of 3·9 g (0·01 mole) potassium anhydrobiisatate in 10 ml water was cooled (5°) and treated, in portions, with a slight excess of 5% HCl. The precipitate was immediately filtered and washed with ice-cold water to give 2·8 g (89·7%) of colourless *anhydrobiisatic acid* (IVa). It was purified by dissolving it in ether and precipitating with petroleum ether. M.p. 176° (dec). Equivalent, found:* 156·1; calc. 156·1. pK_1 (water) 2·88. (Found: C, 61·37; H, 3·83; N, 9·10; $C_{16}H_{12}O_5N_2$ requires: C, 61·54; H, 3·87; N, 8·97%).

Hydrolysis of anhydrobiisatic acid. A solution of 3·1 g (0·01 mole) acid (IVa) in 20 ml water, on refluxing turned red and, on evaporation, gave quantitatively (2·9 g) pure isatin, m.p. 198° (alone or mixed with authentic sample).

Anhydrobiisatic acid dimethyl ester (IVb). A solution of 12·5 g (0·04 mole) anhydrobiisatic acid (IVa) in 250 ml anhydrous ether was cooled (5°) and treated dropwise with a slight excess of ethereal diazomethane. The *dimethyl ester* (IVb), which precipitated from the solution, was filtered (13 g; 95·6%) and recrystallized from ethanol. M.p. 238°. Saponification value,[22] found: 328·4; calc. 329·7; Mol. wt., found:† 336·1; calc. 340·3. (Found: C, 63·58; H, 4·79; N, 8·21; $C_{18}H_{16}O_5N_2$ requires: C, 63·52; H, 4·74; N, 8·23%).

Saponification of anhydrobiisatic acid dimethyl ester. The ester (IVb) (0·68 g; 0·002 mole) was refluxed (30 min) with 16 ml 0·5 N KOH. The mixture was cooled (5°) and cautiously acidified with 3·64 ml of 2·5 N HCl. Filtration of the precipitate gave 0·514 g (82·3%) of anhydrobiisatic acid (IVa), m.p. 176° (alone or mixed with an authentic sample of the acid).

N:N'-*Dimethylanhydrobiisatic acid* (6:12-*oxa*-5:6:11:12-*tetrahydro*-5:11-*dimethylphenhomazine*-6:12-*dicarboxylic acid*) *and derivatives*

N:N'-*Dimethylanhydrobiisatic acid* (IVc). (a) *Anhydrous.* A mixture of 21g (0·04 mole) silver anhydrobiisatate, 17 g methyl iodide and 200 ml anhydrous ether was refluxed (6 hr) (excluding atmospheric moisture). Silver iodide, was filtered off and washed with ether (5 × 50 ml). The

* This and later equivalents were determined in aqueous or ethanolic solution, by titration with 0·1 N aqueous KOH and using phenolphthalein as indicator.

† The molecular weights were determined by the Rast cryoscopic method.

[22] A. Grün, *Analyse der Fette und Wachse* Band I, p. 147. Springer, Berlin (1925); R. T. Hall and W. E. Shaeffer, *Organic Analysis* Vol. 2, pp. 25–27. Interscience, New York (1954).

filtrate and the washings were combined and evaporated to dryness under reduced pressure, and the crude N:N′-*dimethylanhydrobiisatic acid* (IVc) (12·4 g; 91·5%) was recrystallized from ethyl acetate. M.p. 154° (dec.). Equivalent, found: 170·2; calc. 170·2. pK_1 (ethanol) 3·92. (Found: C, 63·12; H, 5·14; N, 8·02; $C_{18}H_{16}O_5N_2$ requires: C, 63·52; H, 4·74; N, 8·23%).

(b) *Hydrated.* A solution of 19·4 g (0·05 mole) potassium anhydrobiisatate in 100 ml water was placed in a three-necked round-bottomed flask equipped with a stirrer, thermometer and dropping funnel, and the contents of the flask were cooled to 10°. Dimethyl sulphate (12·6 g; 0·1 mole) was added in one portion with stirring, followed by 20% aqueous KOH, which was added at such a rate as to maintain the reaction mixture weakly alkaline. When the solution became permanently alkaline, the solution was allowed to stand (30 min) at room temp. It was then cooled (5°) and acidified with a small excess of 5% HCl. The solid which separated (16·7 g; 88·8%) was purified by dissolving in ethanol, at room temp., and precipitating with water. The pure N:N′-*dimethylanhydrobiisatic acid* (IVc) thus obtained was colourless, m.p. 118° (dec.) and crystallized with two molecules of water. Equivalent, found: 188·6; calc.: 188·2 (Found: C, 57·34; H, 5·38; N, 7·68; $C_{18}H_{16}O_5N_2 \cdot 2H_2O$ requires: C, 57·44; H, 5·36; N, 7·44%).

Conversion of anhydrous acid (IVc) *m.p.* 154°, *to the hydrated acid* (IVc) *m.p.* 118°. The anhydrous acid (IVc) (0·34 g; 0·001 mole), m.p. 154°, was dissolved in 10 ml of 3% aqueous sodium bicarbonate. Acidification of the cooled solution (at 5°) with a small excess of 5% HCl gave 0·35 g (93·1%) of hydrated acid IVc, m.p. 118° (alone or on admixture with an authentic sample obtained as described above). Equivalent, found: 186·5; calc. 188·2.

Hydrolysis of N:N′-*dimethylanhydrobiisatic acid.* A solution of 3·8 g (0·01 mole) acid IVc, m.p. 118°, in 20 ml water soon turned red on refluxing and, on evaporation, gave quantitatively (3·2 g) N-*methylisatin*, m.p. 132° (alone or on admixture with an authentic sample, m.p. 132°[23]).

Silver salt of N:N′-*dimethylanhydrobiisatic acid.* A solution of 11·3 g (0·03 mole) of N:N′-dimethylanhydrobiisatic acid (IVc), m.p. 118°, in 60 ml N aqueous KOH was treated with 11·2 g silver nitrate in 100 ml water. The colourless *silver salt* was filtered and washed with water. (Found: Ag, 38·88 and 38·74. $C_{18}H_{14}O_5N_2Ag_2$ requires: Ag, 38·94%).

N:N′-*Dimethylanhydrobiisatic acid dimethyl ester* (IVd). (a) A cold (5°) suspension of 18·8 g (0·05 mole) of acid IVc, m.p. 118°, in 250 ml anhydrous ether was treated, in portions, with a small excess of ethereal diazomethane. After 2 hr at room temp., the solution was evaporated *in vacuo* and the crude *dimethyl ester* IVd (18·4 g) was crystallized from ethanol. m.p. 173°. Saponification value,[22] found: 304·8; calc. 304·6. Mol. wt. found: 362·2; calc. 368·4. (Found: C, 65·44; H, 5·41; N, 7·57; $C_{20}H_{20}O_5N_2$ requires: C, 65·21; H, 5·47; N, 7·61%).

(b) A mixture consisting of 2·77 g (0·005 mole) silver salt of N:N′-dimethylanhydrobiisatic acid, 2·13 g methyl iodide and 20 ml anhydrous ether was refluxed for 6 hr (exclusion of atmospheric moisture). Silver iodide was filtered, washed with ether (4 × 20 ml), and the filtrate and the washings were evaporated to dryness, under reduced pressure. After crystallization from ethanol, the *dimethyl ester* IVd m.p. 172·5°, alone or mixed with a specimen prepared according to (a).

(c) The acid IVc (1·88 g; 0·005 mole), m.p. 118°, was neutralized with 12 ml of 5% aqueous KOH. To the resulting solution, cooled to 10°, 1·26 g (0·01 mole) of purified dimethyl sulphate was added in one portion, followed by 20% aqueous KOH, at such a rate as to keep the reaction mixture weakly alkaline. When the aqueous solution became permanently alkaline, the addition of KOH was stopped and the mixture allowed to stand (30 min) at room temp. The *dimethyl ester* IVd, which separated (1·55 g; 84·2%), was filtered and crystallized from ethanol. It melted at 173°, whether alone or on admixture with samples of esters prepared as described in (a) or (b).

Saponification of ester IVd. The dimethyl ester IVd (0·184 g; 0·0005 mole) was refluxed for one hour with 4 ml 0·5 N aqueous KOH. The mixture was cooled to 5° and cautiously acidified with 0·91 ml 2·5 N HCl. Filtration of the precipitate gave 0·180 g (95·7%) of N:N′-dimethylanhydrobiisatic acid (IVc), m.p. 118° (alone or mixed with an authentic sample).

Resolution of DL-N:N′-*dimethylanhydrobiisatic acid* (IVc) *into optically active components*

(a) *Diastereoisomeric brucine salts of* IVc. N:N′-Dimethylanhydrobiisatic acid (18·8 g; 0·05 mole), m.p. 118°, was dissolved in 700 ml ethanol and mixed with a solution of 19·7 g (0·05 mole) brucine in 700 ml ethanol. After 4 hr at room temp., the precipitate was filtered (20·8 g) and triturated

[23] M. Kohn and A. Ostersetzer, *Mh. Chem.* **34**, 787 (1913); *Ibid.* **37**, 25 (1916).

5 times with ethanol (5 × 200 ml) to give 18·2 g of *brucine salt of* (−)-N:N′-*dimethylanhydrobiisatic acid*, m.p. 154°. $[\alpha]_{20}^{D} = -38{\cdot}3°$ ($c = 0{\cdot}60$, water). Further washing with ethanol did not raise the melting point of the product nor change the rotation. Crystallization from ethanol was not possible because the acidic salt, like the acid itself, decomposed readily on heating in ethanol.

The ethanolic filtrate, obtained on filtration of the crude salt (but not the washings), was concentrated to 200 ml, under reduced pressure and at temp. below 40°. After standing at 0°, 8·6 g of *brucine salt of* (+)-N:N′-*dimethylanhydrobiisatic acid*, m.p. 171–172°, was obtained. $[\alpha]_{20}^{D} = +20{\cdot}8°$ ($c = 1{\cdot}92$, ethanol).

(b) *Isolation of* (−)- *and* (+)-N:N′-*dimethylanhydrobiisatic acids*. The diastereoisomer insoluble in ethanol (9·175 g; 0·0125 mole), m.p. 154°, was dissolved in 27·5 ml of N aqueous KOH and the resulting solution was diluted with water to 100 ml. After removal of brucine by chloroform extraction (5 × 50 ml), the aqueous layer was cooled to 5° and acidified with a slight excess of 5% HCl. Crystallization of the precipitate from ethanol–water afforded 2·87 g (62·4%) of (−)-N:N′-*dimethylanhydrobiisatic acid* (IVc), m.p. 115–116°. $[\alpha]_{20}^{D} = -50{\cdot}6°$ ($c = 3{\cdot}00$, ethanol). (Found: C, 57·18; H, 5·33; N, 7·28; $C_{18}H_{16}O_5N_2{\cdot}2H_2O$ requires: C, 57·44; H, 5·36; N, 7·44%).

The diastereoisomer soluble in ethanol (3·67 g; 0·005 mole), m.p. 171–172°, was dissolved in 11·0 ml of N aqueous KOH. Treatment as above gave 1·08 g (60·4%) of (+)-N:N′-*dimethylanhydrobiisatic acid* (IVc), m.p. 114°. $[\alpha]_{20}^{D} = +51{\cdot}3°$ ($c = 3{\cdot}00$, ethanol). (Found: C, 57·07; H, 5·24; N, 7·46. $C_{18}H_{16}O_5N_2{\cdot}2H_2O$ requires: C, 57·44; H, 5·36; N, 7·44%).

Both acids crystallized with two molecules of water. They were soluble in 3% aqueous sodium bicarbonate, and could be reprecipitated unchanged from such solutions with dilute acids. By heating their aqueous solution, both acids were converted quantitatively to N-methylisatin.

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CONSTITUTION OF PINASTRIC ACID

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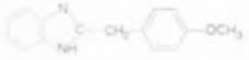
Abstract—New observations in support of the revised constitution[1] for pinastric acid based on a study of its reactions with *o*-phenylene diamine, dimethylaniline, and oxidation with sodium periodate.

THE revised constitution[1] of pinastric acid (I) was based on its reaction with *o*-phenylene diamine and this conclusion would be correct only when two conditions are satisfied: (i) the ester grouping only is attacked by *o*-phenylene diamine in preference to the lactone group; (ii) under the experimental conditions there should be no possibility of the hydroxy ester grouping yielding a lactone by elimination of methanol. Previous experiments[1,2] have not excluded both possibilities though indicating that the ester methoxyl is lost. It has now been observed that when pinastric acid is heated with dimethylaniline at 210° it gives no dilactone. Hence the loss of the methoxyl group in the presence of *o*-phenylene diamine is due to condensation with it. *p*-Methoxy-pulvinic dilactone when treated with one, two or three moles of *o*-phenylene diamine gave the same intermediate (III) as that formed by pinastric acid, and III when subjected to fission with alcoholic potash yielded 2-(*p*-methoxy-benzyl)-benziminazole(V). This indicated that under the conditions employed, only the lactone ring near the *p*-methoxy-phenyl group opens, and when one ring has been opened the other is stable. The course of the reaction is in agreement with the explanations given by Mittal and Seshadri.[1] If under the conditions of the reaction of pinastric acid with *o*-phenylene diamine the second lactone ring is closed it will be the one to be preferentially opened again and will not make any difference in the final result. In order to remove this possibility and to understand the course of the reaction, the methyl ether (II) of pinastric acid has been condensed with *o*-phenylene diamine yielding a product (IV) having two methoxyl groups and providing proof that the ester group alone has reacted and that the lactone ring is not involved. When subjected to fission with alcoholic potash it gave 2-(*p*-methoxybenzyl)-benziminazole (V).

I, R = H
II, R = CH_3

III, R = $C_6H_4OCH_3(p)$; R' = C_6H_5; R'' = H
IV, R = $C_6H_4OCH_3(p)$; R' = C_6H_5; R'' = CH_3

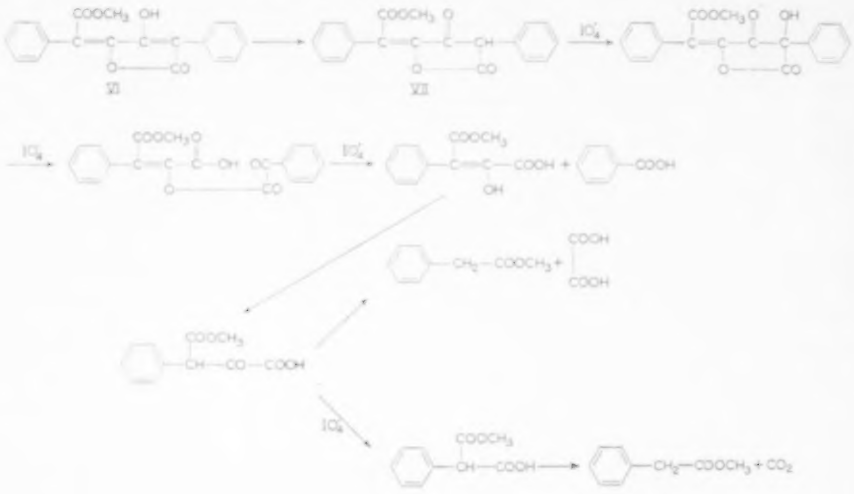


V

Additional evidence for the structure of pinastric acid has been obtained by oxidising the acid with sodium periodate. A preliminary investigation was carried out by

[1] O. P. Mittal and T. R. Seshadri, *J. Chem. Soc.* 3053 (1955).
[2] A. Schonberg and A. Sina, *J. Chem. Soc.* 601 (1946).

oxidising vulpinic acid (VI) of similar constitution with sodium periodate. Benzoic acid and methyl phenylacetate were obtained, and in the case of pinastric acid benzoic acid and methyl *p*-methoxyphenylacetate were identified. In both cases oxalic acid was identified by paper chromatography. Pinastric acid methyl ether (II) when treated with sodium periodate was recovered unchanged. The diketonic structure (VII) is essential for the fission of pinastric acid on oxidation.[3]



EXPERIMENTAL

Action of heat on pinastric acid (I). Pinastric acid (0·1 g) and dimethylaniline (10 cc) were heated (oil bath) at 200–210° for 3 hr. After cooling, the mixture was poured into ice and HCl, and the pale orange solid filtered. It was soluble in aqueous sodium bicarbonate. After drying it crystallized from benzene and light petroleum as orange rectangular plates, m.p. 202–204°. The mixed m.p. with an authentic sample of pinastric acid was undepressed.

Condensation of 4-methoxy pulvinic dilactone and o-phenylene diamine. 4-Methoxy-pulvinic dilactone (1 g), *o*-phenylene diamine (0·54 g, 1 mole) and dimethylaniline (25 cc) were heated (oil bath) under reflux at 200–210° (4 hr). After cooling the mixture was poured into ice and HCl. The dark brown solid was filtered and washed with dilute HCl and then with water. It was dried and crystallized from a mixture of ethyl acetate and light petroleum, yielding brown red rhombohedral plates melting (dec) at 292–294° (0·35 g). The mixed m.p. with a sample obtained by the condensation of pinastric acid with *o*-phenylene diamine was undepressed. The same product was obtained when the dilactone was treated with two or even three moles of *o*-phenylene diamine. The poor yields in this reaction is due to the formation of resinous matter.

Hydrolysis. The above product (0·3 g) was heated under reflux with alcoholic potash (15 cc 15%) for 5 hr. The insoluble potassium salts were filtered and alcohol removed under reduced pressure. The dried solid cyrstallized from a mixture of ethyl acetate and light petroleum (40–60°) as colourless shining rectangular plates, m.p. 165–67° alone or admixed with a sample of 2-*p*-methoxy-benzyl-benziminazole (V).

Condensation of pinastric acid methyl ether (II) *and o-phenylene diamine*. Pinastric acid methyl ether (0·7 g), *o*-phenylene diamine (0·54 g) and dimethylaniline (31 cc) were heated under reflux for 4 hr. The product was worked up as above. It yielded brown red rhombohedral prisms melting with decomposition at 284° (0·3 g) (Found: C, 73·7; H, 5·1; OCH_3, 12·3; N, 6·2; $C_{26}H_{20}O_4N_2$ requires: C, 73·6; H, 4·7; OCH_3 12·4; N, 6·6%). Methoxyl estimation by Ziesel's method repeatedly gave low value. This seemed to be due to part of methyl group migrating to nitrogen.

[3] M. L. Wolfrom and J. M. Bobbit, *J. Amer. Chem. Soc.* **78**, 2489 (1956).

Hence for the methoxyl estimation Ziesel procedure was followed by Herzig-Meyer procedure and the total was found to give the correct value as recorded above.

Hydrolysis. The above product (0·3 g) was heated under reflux with alcoholic potash (15 cc, 15%) for 5 hr. The product when worked up crystallized from a mixture of ethyl acetate and light petroleum as colourless shining rectangular plates, m.p. 165–167°. The mixed m.p. with 2-*p*-methoxy-benzyl-benziminazole (V) was undepressed.

Oxidation of C_{19} compounds with sodium periodate: vulpinic acid (VI). Vulpinic acid (0·5 g) was dissolved in alcohol (150 cc) and an aqueous solution of sodium periodate (5 moles, 1·65 g) added. The solution was allowed to stand at room temp for 30 hr. Alcohol was distilled under reduced pressure and water added to the residue. The aqueous solution was saturated with NaCl and extracted repeatedly with ether. The ether solution was extracted repeatedly with aqueous sodium bicabonate (fraction A); subsequent extraction with 1% aqueous sodium hydroxide removed nothing. The remaining solution containing the neutral fraction was dried over anhydrous sodium sulphate. On evaporation a yellow oil was obtained, which was heated under reflux with aqueous sodium hydroxide (20 cc, 5%) for ½ hr. The solution after cooling was acidified with dilute HCl and extracted repeatedly with ether. On evaporating the ether a semi-solid was obtained, the *p*-toluidide of which after crystallization (0·1 g) had the m.p. 135–136° alone or admixed with the *p*-toluidide of phenylacetic acid.

Fraction A was acidified with dilute HCl, saturated with NaCl and extracted repeatedly with ether. The ether solution after drying and evaporation yielded a semi-solid, a portion of which when sublimed in vacuum gave colourless needles (0·04 g), m.p. 120–121° undepressed by benzoic acid. The second portion was subjected to paper chromatography using butanol saturated with ammonia as the irrigating solvent and bromophenol blue as the indicator. It showed two rings having R_f value 0·59 and 0·30 at 30°. Benzoic acid and oxalic acid when run separately under the same conditions gave R_f values 0·59 and 0·30 respectively.

Pinastric acid (I). Pinastric acid (0·5 g) in alcohol was treated with sodium periodate (5 moles, 1·5 g). The product when worked up as in the previous case gave two fractions: (i) the sodium bicarbonate soluble fraction yiedled on vacuum sublimation colourless needles (80 mg), m.p. 120–121° alone or admixed with a sample of benzoic acid. The crude product when subjected to circular paper chromatography under the conditions given above gave two rings having R_f value 0·59 and 0·30 at 30° agreeing with those of benzoic acid and oxalic acid respectively; (ii) the neutral fraction yielded a yellow oil which when hydrolysed with aqueous alkali gave a semi-solid, the amide of which (80 mg, m.p. 175–177°) agreed in all its properties with the amide of *p*-methoxy-phenylacetic acid.

Pinastric acid methyl ether (II). The methyl ether (0·3 g) was dissolved in alcohol (200 cc) and sodium periodate (5 moles, 1·4 g) in water added and the solution allowed to stand for 30 hr. The sodium bicarbonate and 1% sodium hydroxide fractions did not yield anything. The neutral fraction yielded yellow stout rhombohedral prisms, m.p. 150–151° undepressed by pinastric acid methyl ether.

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HETEROCYCLIC FLUORINE COMPOUNDS—III*

MONOFLUOROXANTHONES

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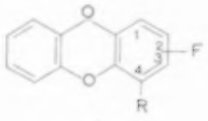
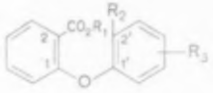
Abstract—The four monofluoroxanthones substituted in the benzene ring have been prepared by two different routes, namely by cyclisation of the appropriate carboxyfluorodiphenyl ether and by a Balz–Schiemann reaction with the corresponding aminoxanthone.

1-FLUORO-, 2-fluoro-, 3-fluoro-, and 4-fluoroxanthone (as I; R = H) have been made by cyclisation of the requisite carboxyfluorodiphenyl ether obtained by an Ullman type of condensation between a fluorophenol and *o*-chlorobenzoic acid. The crude diphenyl acid was purified by conversion into its methyl ester followed by hydrolysis. Concentrated sulphuric acid proved the best cyclising agent for fluoroxanthone formation. Cyclisation of 2-carboxy-3′-fluorodiphenyl ether (II; $R_1 = R_2 = H$, $R_3 = F$) gave a mixture of 1-fluoro- and 3-fluoroxanthone in a ratio of 1 : 3. The formation of a large excess of the 3-fluoroisomer is probably due to the strong *para*-directing influence of fluorine which has also been observed with the fluoroindoles.[1] The mixture was readily separated by fractional crystallisation from boiling ethanol followed by chromatography. 1-Fluoroxanthone needed as a reference compound



I



II

was made unambiguously from 1-fluoro-4-methylxanthone (I; R = Me) obtained by cyclisation of 2-carboxy-5′-fluoro-2′-methyldiphenyl ether (II; $R_1 = H$, $R_2 =$ Me, $R_3 = F$) in which the methyl group prevents ring closure from occurring in two directions. Attempts to oxidise the methylgroup with alkaline potassium permanganate or sodium dichromate in sulphuric acid resulted in destruction of the xanthone ring, but were successful when chromium trioxide dissolved in a mixture of acetic and sulphuric acid at 40° was employed. Decarboxylation of the resulting 4-carboxy-1-fluoroxanthone (I; $R = CO_2H$) occurred readily on heating the acid to its melting point. Authentic 3-fluoroxanthone was prepared from 2-carboxy-5-fluorodiphenyl ether in the usual way.

Another route to the monofluoroxanthones was by a Balz–Schiemann reaction with the monoaminoxanthones. The required nitroxanthones resulted from cyclisation of nitrodiphenyl ethers of type II ($R_1 = R_2 = H$, $R_3 = NO_2$). When the 3′-substituted diphenyl ether was ringclosed, a mixture of two xanthones (1-nitro and

* Part II was published in *J. Chem. Soc.* 1283 (1955).

[1] F. L. Allen, J. C. Brunton and H. Suschitzky, *J. Chem. Soc.* 1283 (1955).

3-nitro) was obtained, from which 1-nitroxanthone was separable by fractional crystallisation. This nitrocompound was also prepared unambiguously from 2-carboxy-3-nitrodiphenyl ether.

Absorption spectra of the fluorine substituted xanthones are given in the accompanying table.

TABLE 1. ULTRA-VIOLET ABSORPTION MAXIMA (mμ) IN METHANOL

Xanthones	λ_1	ϵ_1	λ_2	ϵ_2	λ_3	ϵ_3	λ_4	ϵ_4
1-F	238	42,000	263	11,800	—	—	336	6170
2-F	230 240	31,900 30,400	259	11,200	290	4200	342	7200
3-F	233	44,800	258	11,550	283	7220	329	6450
4-F	238	41,000	262	12,400	327	5800	337	6400
1-F-4-Me	241	40,400	268	9600	—	—	340	5900

EXPERIMENTAL

Fluoromethoxycarbonyldiphenyl ethers. Sodium (2 moles) was dissolved in 40 times its weight of methanol and to this solution was added the requisite fluorophenol (1 mole), *o*-chlorobenzoic acid (1 mole) and a trace of copper powder. After driving off the methanol the reaction mixture was kept at 150° for 2 hr and finally heated to 200° for 20 min. Extraction of the reaction mixture with boiling water followed by acidification of the filtrate yielded a crude carboxyfluorodiphenyl ether which was esterified with methanol and sulphuric acid by refluxing for 8 hr. The excess of methanol was distilled off, the residue poured into ice and the crude ester extracted with ether and finally purified by fractional distillation.

2'-Fluoro-2-methoxycarbonyldiphenyl ether (40%), b.p. 146°/3 mm (Found: C, 68·2; H, 4·5; $C_{14}H_{11}O_3F$ requires: C, 68·3; H, 4·5%).

3'-Fluoro-2-methoxycarbonyldiphenyl ether (32·5%), b.p. 145°/4 mm (Found: C, 68·2; H, 4·4%).

4'-Fluoro-2-methoxycarbonyldiphenyl ester (44%), b.p. 154°/4 mm (Found: C, 68·0; H, 4·4%).

5-Fluoro-2-methoxycarbonyldiphenyl ether was obtained by condensation of 2-chloro-4-fluorobenzoic acid[2] and phenol with sodium as a pale-yellow oil (30%) b.p. 158°/6 mm (Found: C, 68·2; H, 4·4%).

5'-Fluoro-2-methoxycarbonyl-2'-methyldiphenyl ether. A solution of 2-amino-4-fluorotoluene (10 g) in concentrated sulphuric acid (30·6 g) and water (93 ml) was diazotised and then added in small portions to a boiling, saturated solution of copper sulphate (150 ml). Steam distillation of the reaction mixture gave 4-fluoro-2-hydroxytoluene as a light-amber oil (90%), b.p. 66°/4 mm. (Found: C, 66·4; H, 5·4. C_7H_7OF requires: C, 66·7; H, 5·5%). Its p-*nitrobenzoyl ester* made in pyridine had m.p. 113° (Found: C, 61·0; H, 3·8. $C_{14}H_{10}O_4NF$ requires: C, 61·1; H, 3·6%). Condensation of the phenol with *o*-chlorobenzoic acid as described above gave *5'-fluoro-2-methoxycarbonyl-2'-methyldiphenyl ether* (35%) b.p.128°/2 mm (Found: C, 69·5; H, 5·2; $C_{15}H_{13}O_3F$ requires: C, 69·2; H, 5·0%).

Carboxyfluorodiphenyl ethers were obtained pure in high yield by hydrolysis of the above esters (5 g) with N-potassium hydroxide (100 ml). The compounds thus prepared and their *p*-nitrobenzyl esters are listed in Table 2.

Fluoroxanthones

Method A: The requisite carboxyfluorodiphenyl ether was cyclised by heating with about 15 times its weight of concentrated sulphuric acid on a water-bath for 0·5 hr. The reaction mixture was poured onto ice and the precipitated fluoroxanthone washed with caustic soda and recrystallised from ethanol.

[2] O. Yu. Magidson and A. I. Travin, *J. Gen. Chem. (U.S.S.R.)* **11**, 243 (1941).

Method B: The requisite aminoxanthone[3] prepared from 1-nitro,[3,4] 2-nitro,[2,5] 3-nitro,[2,5] and 4-nitroxanthone[6] was converted into its diazonium borofluoride which was decomposed in the usual way[7] to give a fluoroxanthone.

1-Fluoroxanthone

Method A: This compound was unambiguously made by cyclisation of 2-carboxy-5′-fluoro-2′-methyldiphenyl ether which gave *1-fluoro-4-methylxanthone* (66·5%), m.p. 156–157° (Found: C, 73·3; H, 4·0. $C_{14}H_9O_2F$ requires: C, 73·7; H, 4·1%). The methylxanthone (2·4 g) dissolved in a mixture of acetic acid (50 ml) and concentrated sulphuric acid (25 ml) was oxidised by slow addition of an aqueous solution (30 ml) of chromium trioxide (6 g) at 40°. When the reaction mixture was

TABLE 2. 2-CARBOXYDIPHENYL ETHERS

Substituent	M.P. C°	Found (%) C	H	Formula	Required (%) C	H
2′-Fluoro	140	67·2	4·1	$C_{13}H_9O_3F$	67·2	3·9
3′-Fluoro	130	66·8	3·7	$C_{13}H_9O_3F$	67·2	3·9
4′-Fluoro	142	67·3	4·1	$C_{13}H_9O_3F$	67·2	3·9
5-Fluoro	122	67·2	4·0	$C_{13}H_9O_3F$	67·2	3·9
5′-Fluoro-2′-methyl	108	68·6	4·6	$C_{14}H_{11}O_3F$	68·3	4·5
p-NITROBENZYL ESTERS OF 2-CARBOXYDIPHENYL ETHERS						
2′-Fluoro	75	65·3	3·8	$C_{20}H_{14}O_5NF$	65·4	3·8
3′-Fluoro	54	65·6	4·3	$C_{20}H_{14}O_5NF$	65·4	3·8
4′-Fluoro	76	65·4	4·1	$C_{20}H_{14}O_5NF$	65·4	3·8
5′-Fluoro	112	65·5	4·1	$C_{20}H_{14}O_5NF$	65·4	3·8
5′-Fluoro-2′-methyl	87	66·0	4·3	$C_{21}H_{16}O_5NF$	66·1	4·2

poured onto ice, *4-carboxy-1-fluoroxanthone* precipitated as white crystals (92%), m.p. 252° (dec) (Found: C, 64·9; H, 2·9. $C_{14}H_7O_4F$ requires: C, 65·1; H, 2·7%). Its *p-nitrobenzyl ester* had m.p. 170–172° (Found: C, 63·7; H, 3·2; N, 3·9. $C_{21}H_{12}O_6NF$ requires: C, 64·1; H, 3·1; N, 3·6%). On heating the acid (0·5 g) in an ignition tube until gas evolution ceased and extraction of the residue with petroleum ether (b.p. 60–80°) *1-fluoroxanthone* was obtained as white needles (6%), m.p. 147° (Found: C, 72·6; H, 3·6. $C_{13}H_7O_2F$ requires: C, 72·9; H, 3·3%). Ring-closure of 2-carboxy-3′-fluorodiphenyl ether gave a mixture of 1-fluoro- (1 part) and 3-fluoroxanthone (3 parts) separable by fractional crystallisation from ethanol in which 3-fluoroxanthone is less soluble. Purification of the constituents was carried out by chromatography on an alumina column with petroleum ether (b.p. 60–80°) as solvent.

Method B: Decomposition of xanthone-1-diazonium borofluoride, m.p. 154° (dec) gave 1-fluoroxanthone (50%), m.p. and mixed m.p. 147°.

2-Fluoroxanthone

Method A gave *2-fluoroxanthone* (83%) as white, feathery needles, m.p. 156° (Found: C, 72·6; H, 3·5%).

Method B: Xanthone-2-diazonium borofluoride, m.p. 181° (dec) gave 2-fluoroxanthone (58%) on decomposition.

[3] A. A. Goldberg and H. A. Walker, *J. Chem. Soc.* 1348 (1953).
[4] C. F. Koelsch and F. J. Lucht, *J. Amer. Chem. Soc.* **71**, 3556 (1949).
[5] F. G. Mann and J. H. Turnbull, *J. Chem. Soc.* 747 (1951).
[6] R. Q. Brewster and F. Strain, *J. Amer. Chem. Soc.* **56**, 117 (1934).
[7] F. L. Allen and H. Suschitzky, *J. Chem. Soc.* 3845 (1953).

3-Fluoroxanthone

Method A: 5-Fluoro-2-methoxycarbonyldiphenyl ether yielded authentic 3-*fluoroxanthone* (75·5%), m.p. 158° (Found: C, 72·7; H, 3·2). This xanthone was also obtained from 2-carboxy-3'-fluorodiphenyl ether (cf. 1-fluoro-xanthone).

Method B: A yield of 45·5% resulted from pyrolysis of xanthone-3-diazonium borofluoride, m.p. 161° (dec).

4-Fluoroxanthone

Method A: Ring-closure of 2-carboxy-2'-fluorodiphenyl ether gave 4-*fluoroxanthone*, m.p. 177° in 76% yield (Found: C, 72·9; H, 3·4%).

Method B: A Balz–Schiemann reaction with xanthone-4-diazonium borofluoride, m.p. 204° (dec) yielded impure fluoroxanthone (21%) which was purified by chromotography.

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STEREOCHEMISTRY OF THE REDUCTION OF TROPINONE

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Abstract—Tropinone has been reduced under various conditions of time, temperature, solvent and reducing agent. The stereoisomeric composition of the reduction product was determined by infra-red spectrophotometry. The results indicate the participation of kinetic and thermodynamic factors in the stereoisomeric course of the reduction, the former depending upon the effective size of the reducing species. An assignment of the order of size of reducing species in particular solvents is made.

The stereoisomeric composition of the product of equilibration is independent of the reagent and the temperature in the system studied.

DURING a general investigation of the stereochemistry of addition to heterocyclic ketones, the stereochemistry of the reduction of tropinone using various reagents and conditions has been examined.

Analytical method. Other workers[1,2] have questioned the accuracy of the analytical procedures used for the analysis of the isomeric mixtures obtained on the reduction of ketones, the results of which have been used as the basis for generalisations on the stereochemistry of the additions to ketones. The infra-red spectrophotometric analytical procedure used in the present investigation constituted an accurate ($\pm$3 per cent) and rapid method for the assay of mixtures of tropine, ψ-tropine and tropinone. The infra-red absorption curves for tropine and ψ-tropine (Fig. 1) show peaks at 958 cm^{-1} and 1020 cm^{-1} respectively, which are free from interference from the other epimer. The assay procedure was based on these peaks (Fig. 2), other stronger peaks being rejected, since the use of these necessitated compensation for a sloping background interference which made the assay inherently less accurate. The tropinone content of the mixtures was determined by plotting a calibration curve (Fig. 3) at 1720 cm^{-1} under the same operating conditions as for the tropines. The absorptions at 958 cm^{-1} and 1020 cm^{-1} were corrected for interference from tropinone (Fig. 3). A check on the accuracy of the assay was obtained by measuring the absorption [E(1%/cm)] at 972 cm^{-1} and 990 cm^{-1}, which are not in the optimum optical density regions. The absorptions were plotted against the percentage tropine/ψ-tropine (tropinone absent) found in the assay. The graph (Fig. 4), the lines on which represent the theoretical absorption for tropine/ψ-tropine mixtures, indicates an accuracy of $\pm$5 per cent. Known mixtures of tropine and ψ-tropine gave results in all cases within the accuracy claimed for the assay. By summation of the quantities of tropine, ψ-tropine and tropinone the relative percentage of each present could be calculated. The recovery as indicated by infra-red absorption was in close agreement with the total base content, (calculated as amino-alcohol) of the mixtures as determined by non-aqueous titration.

[1] R. J. Wicker, *J. Chem. Soc.* 2165 (1956).
[2] E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.* **79**, 5992 (1957).

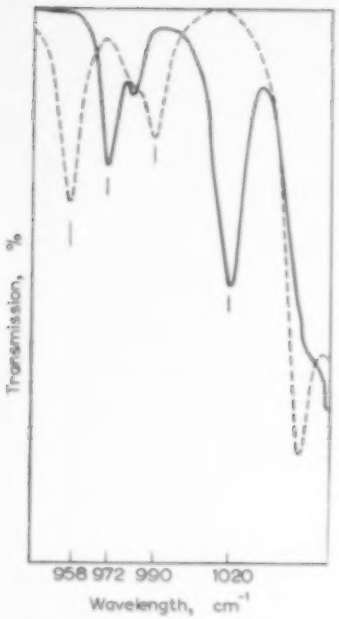

Fig. 1. Infra-red absorption curve for tropine and ψ-tropine in CS_2. (Tropine – – – –, ψ-tropine ——)

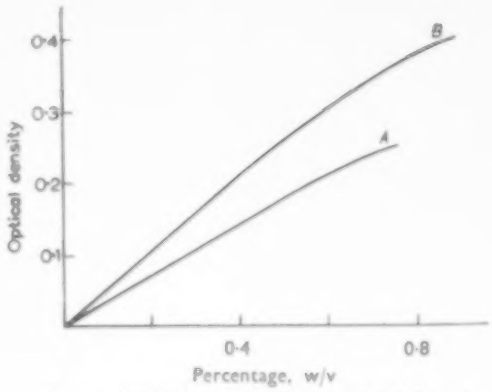

Fig. 2. Calibration curve of tropine (A, 958 cm^{-1}) and ψ-tropine (B, 1020 cm^{-1}).

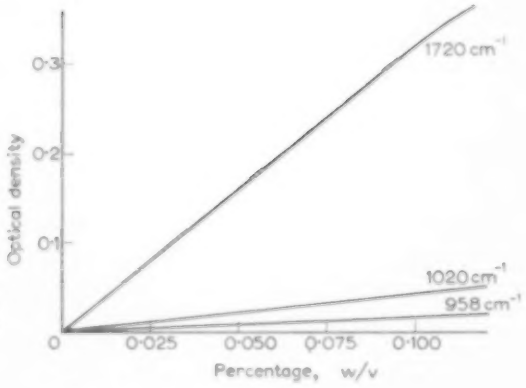

Fig. 3. Calibration curve of tropinone, showing corrections applied to epimeric alcohols for tropinone.

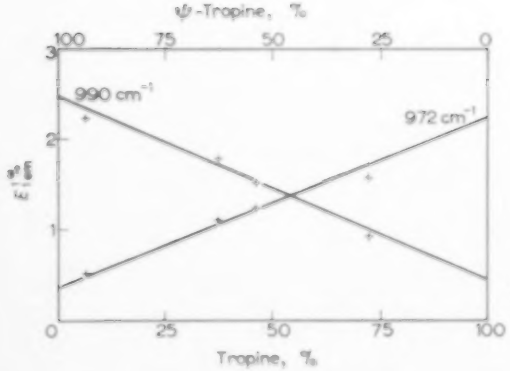

Fig. 4. Theoretical absorption for tropine/ψ-tropine mixtures (+ represents observed absorptions during assay process).

Attempts to determine the composition of the mixtures by chromatography on alumina proved tedious, and although less accurate than the results obtained by the infra-red procedure, qualitatively supported the latter.

Results. The results of the reductions of tropinone are summarised in Table 1.

The equilibration of tropine and ψ-tropine using sodium in *n*-pentanol and *iso*-butanol gave results equivalent with those obtained upon prolonged equilibration using aluminium *iso*propoxide in *iso*propanol; isomerisation involved in a 2·5 hour reduction with the latter reagent will not alter significantly the stereochemical composition of the product of reduction.

Equilibration did not occur using lithium aluminium hydride, sodium borohydride or potassium borohydride even at a temperature of approximately 100°.

The proportion of tropine in the reduction products increased as the following reagents were used: Na/ethanol or *iso*butanol; $NaBH_4$ or KBH_4/water; $NaBH_4$/89% v/v methanol; $LiAlH_4$/ether or tetrahydrofuran; $NaBH_4$/95% v/v methanol; $NaBH_4$ or KBH_4/methanol; $NaBH(OCH_3)_3$/methanol; $Al(OPr^i)_3$/*iso*-propanol.

Using $LiAlH_4$, the change of solvent from ether to tetrahydrofuran gave similar reduction mixtures (Table 1, nos. 1, 5). Changes of the temperature of reduction had negligible effect on the stereochemical course of the reaction using $NaBH_4$ (Table 1, nos. 7, 8), $LiAlH_4$ (Table 1, nos. 1, 5) and sodium in *iso*butanol (Table 1, nos. 26, 27). [Contrast Nace and O'Connor[3] who found that the isomeric composition upon reduction of cholestanone by $LiAlH_4$ and aluminium alkoxides was greatly affected by temperature, and Trevoy and Brown[4] who suggested that lower temperatures increased the "directive effect" on the $LiAlH_4$ reductions of 1:2-diketones].

DISCUSSION

Factors controlling stereochemistry of reduction

The variation in the stereoisomeric composition of the products of reduction of tropinone using various reagents and conditions is explicable in terms of thermodynamic and kinetic contributions in the reaction. This explanation is supported by various studies of additions to the carbonyl group of acyclic, alicyclic and polycyclic ketones,[2,3,5–15] e.g., Jackman *et al.*[5] considered that steric hindrance about the carbonyl group was the chief factor determining the relative amount of isomers obtained in the reduction of alkyl*cyclo*hexanones, Nace *et al.*[3] emphasised the size of the reducing agent in the reduction of cholestanone; both groups mentioned the importance of the relative thermodynamic stability of the isomers in certain cases. Barton[14] emphasised the thermodynamic factor in pointing out that the equatorial isomer was predominant in the product of reductions of alicyclic unhindered ketones. Dauben

[3] H. R. Nace and G. L. O'Connor, *J. Amer. Chem. Soc.* **73**, 5824 (1951).
[4] L. W. Trevoy and W. G. Brown, *J. Amer. Chem. Soc.* **71**, 1675 (1949).
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[6] D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.* **72**, 5743 (1950).
[7] H. L. Goering and C. Serres, Jr., *J. Amer. Chem. Soc.* **74**, 5908 (1952).
[8] D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).
[9] D. J. Cram and F. D. Greene, *J. Amer. Chem. Soc.* **75**, 6005 (1953).
[10] R. Cornubert, G. Barrand, M. Cormier, M. Descharmes and H. G. Eggert, *Bull. Soc. Chim. Fr.* 400 (1955).
[11] W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1956).
[12] J. B. Umland and M. J. Jefraim, *J. Amer. Chem. Soc.* **78**, 2788 (1956).
[13] K. D. Hardy and R. J. Wicker, *J. Amer. Chem. Soc.* **80**, 640 (1958).
[14] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).
[15] J. B. Umland and B. W. Williams, *J. Org. Chem.* **21**, 1302 (1956).

Table 1.—Isomeric composition of mixtures of tropine and ψ-tropine (and tropinone) upon reduction of tropinone

Reducing agent	Temp.	Time (hr)	Percentage			Total base content %	
			ψ-Tropine	Tropine	Tropinone	A*	B*
1. $LiAlH_4$ ether	Reflux	0·5	54	45	1	96	97
2. $LiAlH_4$ ether	Reflux	5·0	54·5	45·5	—	92	97
3. $LiAlH_4$ ether (a)	Reflux	3·0	57	43	—	91	92
4. $LiAlH_4$ ether (b)	Reflux	1·0	56·5	41	2·5	91	93
5. $LiAlH_4$ tetrahydrofuran	Reflux	5·0	57	42	1	92	92
6. $NaBH_4$ water	20°	2·0	65	34	1	87	89
7. $NaBH_4$ water	20°	24·0	72	28	—	97	97
8. $NaBH_4$ water	Reflux	48·0	69	30	1	95	94
9. $NaBH_4$ water (c)	20°	2·0	70	29	1	97	99
10. $NaBH_4$ 25% v/v methanol	20°	7·0	68	32	—	87	85
11. $NaBH_4$ 89% v/v methanol	20°	16·0	60	40	—	94	97
12. $NaBH_4$ 95% v/v methanol	Reflux	6·0	51	49	—	99	98
13. $NaBH_4$ 100% v/v methanol	Reflux	6·0	48	52	—	92	94
14. $NaBH_4$ ethanol	Reflux	6·0	52	48	—	97	96
15. $NaBH_4$ *n*-butanol	Reflux	6·0	58	42	—	99	96
16. $NaBH_4$ *iso*propanol	Reflux	2·25	67	33	—	98	97
17. KBH_4 water	20°	24·0	66	34	—	92	93
18. KBH_4 methanol	Reflux	6·0	44	55	1	89	90
19. $LiBH_4$ tetrahydrofuran	Reflux	5·0	66	34	—	90	89
20. $NaBH(OCH_3)_3$ water	20°	24·0	54	39	7	82	88
21. $NaBH(OCH_3)_3$ water	Reflux	48·0	59	41	—	90	90
22. $NaBH(OCH_3)_3$ methanol	Reflux	6·0	37	59	—	94	96
23. $Al(OPr^i)_3$ *iso*propanol (d)	Reflux	2·5	34	65	1	81	91
24. $Al(OPr^i)_3$ *iso*propanol (d)	Reflux	1·5	29	71	—	92	91
25. Na/C_2H_5OH/toluene	Reflux	3·0	85	11	4	95	95
26. Na/*iso* C_4H_9OH/toluene	Reflux	3·0	88	9	3	94	93
27. Na/*iso* C_4H_9OH/toluene	0°	18·0	89	7	4	98	96
28. Na/*iso* C_4H_9OH/toluene	0°	18·0	84	10	6	96	96
29. $Al(OPr^i)_3$ equilibration "Tropine" (e)	Reflux	20	36	60	4	86	90
30. $Al(OPr^i)_3$ equilibration "Tropine" (e)	Reflux	40	54	43	3	90	88
31. $Al(OPr^i)_3$ equilibration "Tropine" (e)	Reflux	288	83·5	16·0	0·5	102	95
32. $Al(OPr^i)_3$ equilibration "Pseudotropine"	Reflux	40	93	6	1	96	96
33. $Al(OPr^i)_3$ equilibration "Pseudotropine"	Reflux	288	88	11	1	93	92
34. Na/*n*-pentanol equilibration $LiAlH_4$ reduction product (f)	Reflux	3	84	15	1	92	93
35. Na/*n*-pentanol equilibration "Tropine" (e)	Reflux	12	91	8	1	96	93
36. Na/*n*-pentanol equilibration "Pseudotropine"	Reflux	12	88	11	1	92	92
37. Na/*iso*butanol equilibration Tropine	0°	18	14	81	5	86	91

(a) 4 moles $LiAlH_4$: 1 mole tropinone.
(b) ¼ mole $LiAlH_4$: 1 mole tropinone.
(c) Inverse addition.
(d) Figure slightly higher than true value since slow equilibration occurs subsequent to amino-alcohol production.
(e) "Tropine" containing 94% tropine and 6% ψ-tropine.
(f) $LiAlH_4$ reduction product 2.
A*—Total base content of mixture (%) as sum of infra-red determined values.
B*—Total base content of mixture (%) by titration in non-aqueous media (calc. as amino-alcohol).

et al.[11] stated that increase in the effective size of the reducing agent resulted in "steric approach control" assuming an increasingly important role compared with the molecular energetics of product formation, "product development control."

(a) *Thermodynamic factor.* A method of allocation of the relative thermodynamic stabilities of epimeric alcohols involves the measurement of their percentages in the mixture obtained under "equilibrating conditions". The relative importance of factors other than thermodynamic in the reduction of the parent ketone is thus assessed from the departure of the isomeric content of the reduction product from the "equilibrated" values (usually sodium/alcohol equilibration).* Two assumptions are inherent in this treatment, (i) that the difference in energy levels of the isomers under equilibrating conditions does not differ greatly from the difference of the activation energies of the complex of the two forms involved in reduction, and (ii) that differences in equilibrating conditions do not alter the stereoisomeric composition of the product. It seems reasonable to assume however, that changes in the equilibrating conditions may in fact alter the position of equilibration since solvation and alcohol–reagent interaction may alter the apparent relative sizes of the alcoholic group or anion in the two conformations and thus their relative thermodynamic stabilities. The temperature of equilibration could also affect the stereochemical composition. Recently Eliel and Ro[2] have shown that while aluminium *iso*propoxide equilibration of 4*t*-butyl*cyclo*hexanol gave 77–81 per cent of the more stable *trans* isomer, $LiAlH_4$ reductions gave an even greater proportion (91–93 per cent), a case in which the above assumptions would appear to be invalid. Umland and Williams[15] for instance report that reduction of 2-methyl*cyclo*pentanone with sodium in alcohol and equilibration of the alcohol with aluminium *iso*propoxide gave different results (see also Huckel[16]); Hardy and Wicker[13] consider that reduction with sodium in alcohol will not always yield the "equilibration mixture" and have stressed the importance of the temperature of the reduction.

The present investigation of the equilibration of tropine and ψ-tropine indicates that different reagents, e.g. aluminium *iso*propoxide in *iso*propanol and sodium in *n*-pentanol (Table 1, nos. 33, 36) give products of similar composition which are in general agreement with the isomeric ratios obtained by the sodium in ethanol or sodium in *iso*propanol reductions of tropinone. Furthermore, Na/alcohol reduction of tropinone at different temperatures gives similar results. It would appear reasonable to assume that the results indicate that equilibration of the ions or the alcohols *per se* is involved and that the effect of the reagent is catalytic.

Equilibration is assumed to proceed via dehydrogenation to an intermediate ketone (or aldehyde) and subsequent reduction.[17,18] In one instance, the intermediate ketone has been shown to be formed in the reaction[19] and Doering and Aschner[20] found that equilibration of (−)-phenylmethylcarbinol using potassium *t*-butoxide was completely inhibited by the exclusion of oxygen, potassium peroxides and carbonyl

*An alternative approach to this problem is to assume that the equilibration results are only a qualitative measure of a directional effect. This directive effect is initiated at the first instant of attack of the C atom of the carbonyl group by the reagent and it may well reflect the difference in energy required to direct the forming $C\text{–}O^-$ moiety into either of the two alternative conformations.

[15] W. Huckel, *Liebigs Ann.* **533**, 1 (1937).

[17] T. Wagner-Jauregg, *Freudenberg, Stereochemie* p. 866. Franz Deuticke, Leipzig (1932).

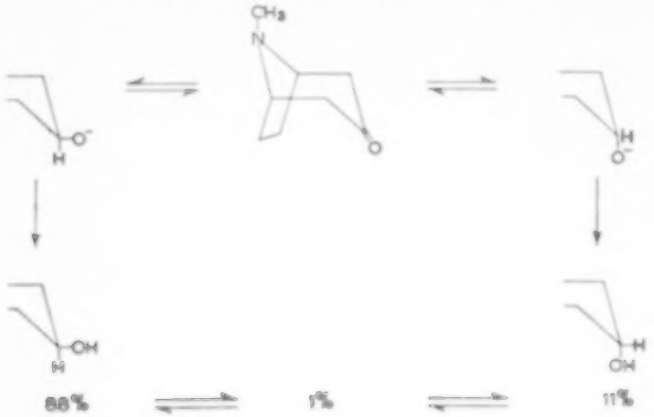
[18] W. Huckel, *Theoretische Grundlagen der Organischen Chemie* Vol. I, p. 286. Akademische Verlagsgesellschaft, Leipzig (1934).

[19] W. Huckel and H. Naab, *Ber. Dtsch. Chem. Ges.* **64**, 2137 (1931).

[20] W. von E. Doering and T. C. Aschner, *J. Amer. Chem. Soc.* **71**, 838 (1949).

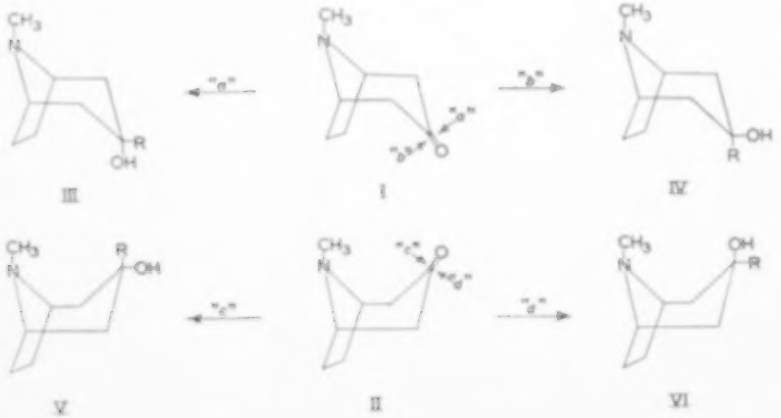
compounds, but that addition of oxidation–reduction systems caused rapid equilibration. In the present work, the ketone (tropinone) has been proved to be present in the products of equilibration of tropine and ψ-tropine using sodium/*n*-pentanol or aluminium *iso*propoxide as equilibrating reagents. (Table 1, nos. 31, 33, 35 and 36).

Since the stereoisomeric proportions are unaffected by the reagents, equilibration of the epimeric alcohols from tropinone may be represented as:—



(b) *Kinetic factor*. The conformation of tropinone in the reaction, the solvent and its effect on the size of the reducing species, the type of the reagent and its mechanism of reaction with the ketone may be considered as potential contributors to the kinetic factor in the reduction.

It seems reasonable to assume that tropinone will exist in a state of dynamic equilibrium between the chair (I) and the boat (II) conformations with probably (I) in major amount. Models indicate that reaction in conformation (I) would result in attack from side "b" being sterically hindered due to the methylene bridge with the resultant kinetic control strongly favouring the production of an alcohol with the hydroxyl group in the tropine conformation (III). Tropinone in conformation (II) would slightly favour attack from side "d" with a consequent kinetic control favouring the predominant formation of the ψ-tropine type alcohol.



VOL. 6 1959

The rate controlling step in the addition of an organometallic reagent to a ketone is considered to be attack of the R^- on the carbon of the carbonyl group. Although full clarification of the mechanism of reduction by complex metal hydrides and alkoxides has not yet been established, there is general agreement that the rate controlling step in reduction is attack by an H^- on the carbonyl carbon. Due to this similarity of mechanism, it would appear reasonable to use as evidence for the conformation of tropinone under nucleophilic attack, the fact that the reaction of phenyl lithium on tropinone gives only one isomer (97%).[21–23] The infra-red spectrum of this alcohol indicates the tropine-type character of the hydroxyl group (type of absorption and lack of intramolecular hydrogen bonding), which establishes that tropinone must have reacted in the chair conformation.

In the reduction of tropinone, steric factors will result in attack from side "a" being less hindered than that from side "b"; however attack from side "a" will require a higher activation energy since the resulting anionic complex will be developed in the thermodynamically less stable axial conformation. Increasing size of reducing species will therefore favour addition to side "a" to yield tropine, if the differences in the activation energies of the two sides of attack upon the carbonyl group are approximately represented by the differences in the energy levels obtained during equilibration. [If the carbonyl oxygen is co-ordinated to a moiety of the reducing agent, i.e. BR_3 of $NaBHR_3$ (or AlH_3 of $LiAlH_4$), increasing size of the co-ordinated group will favour anion formation in the more stable conformation. The formation of a higher proportion of tropine in the reduction product as R is changed from H to OCH_3, indicates that the steric control of the direct attack upon the carbonyl carbon plays a much more important role than carbonyl oxygen co-ordination.]

Reagents and solvents. The order of effective reducing species size of the reagents and solvents suggested from consideration of the stereoisomeric results quoted in Table 1 is $Al/OPr^{iso})_3$/*iso*propanol > $NaBH(OCH_3)_3$/methanol > $NaBH_4$/methanol > $LiAlH_4$/ether > $NaBH(OCH_3)_3$/water > $NaBH_4$/water. This differs from the order given by Dauben *et al.*[11] [$Al(OPr^{iso})_3$ > $NaBH_4$ > $LiAlH_4$] for reduction of 2- and 4-alkyl*cyclo*hexanones. This difference probably arises because these workers did not appear to fully consider the effect of solvent upon the reducing species size; certain anomalies also appear in the published results for the isomeric contents which formed the basis of their conclusions, e.g. the value of 82 per cent *trans*-isomer upon reduction of 2-methyl-*cyclo*hexanone with $LiAlH_4$, since values of 64[6,13] and 60[24] per cent have been reported.[11] A value of 88 per cent, *trans*-isomer in the equilibration of 4- methyl*cyclo*hexanol was used,[11] but Eliel and Ro[2] report a result of 69 and 71 per cent using an infra-red analytical procedure which appears to be inherently more accurate.

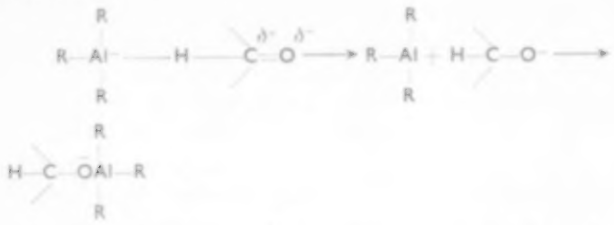
Since the effective reducing species size is the controlling kinetic factor, interaction (either physical or chemical) between the solvent and the reducing agent becomes important. The formation of etherates of $LiAlH_4$[25] and $LiBH_4$[26,27] has been established,

[21] A. H. Beckett, A. F. Casy, G. Kirk and J. Walker, *J. Pharm. Pharmacol.* **9**, 939 (1957).
[22] A. C. Cope and A. A. D'Addieco, *J. Amer. Chem. Soc.* **73**, 3419 (1951).
[23] S. Archer and T. R. Lewis, *Chem. & Ind.* 853 (1954).
[24] A. K. Macbeth and J. S. Shannon, *J. Chem. Soc.* 2852 (1952).
[25] N. G. Gaylord, *Reduction with Complex Metal Hydrides*. Interscience, New York (1956).
[26] G. W. Schaeffer, T. L. Kolski and D. L. Ekstedt, *J. Amer. Chem. Soc.* **79**, 5912 (1957).
[27] T. L. Kolski, H. B. Moore, L. E. Roth, K. J. Martin and G. W. Schaeffer, *J. Amer. Chem. Soc.* **80**, 549 (1958).

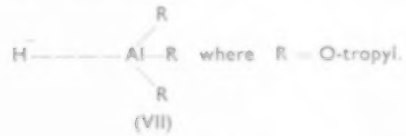
while $NaBH_4$ can be solvated.[28] Little attention appears to have been given to the effect of solvent although Dauben *et al.*[29] have suggested that the solvent may affect the stereochemical composition of the reduction product using $LiAlH_4$.

In the present investigation, it has been established that the solvent will affect the isomeric composition of the reduction product to the greatest extent where chemical reaction between reagent and solvent occurs to produce a new reducing species.

Lithium aluminium hydride. Reduction of a ketone with $LiAlH_4$ is considered to proceed as follows:—



The fact, that a $\frac{1}{4}$ mole $LiAlH_4$ reduces tropinone completely and gives the same isomeric ratio as reduction with 4 moles $LiAlH_4$ indicates not only that all the hydrogen atoms of the reagent are used in the reduction, but also that as the R = H groups of $LiAlH_4$ becomes replaced by R = —O-tropyl groups, the reducing efficiency of the reagent is increased, excess $LiAlH_4$ playing a negligible part in the reaction. Since the size of the reagent increases as the reaction proceeds, one might expect the final reducing species to constitute a very large steric factor (e.g. the change from $NaBH_4$ to $NaBH(OCH_3)_3$ has a profound effect on the stereoisomeric ratio), but the results suggest that this is not the case. It is therefore concluded that in the transfer complex, the more highly substituted aluminohydride constitutes a smaller steric factor than that which its bulk suggests due to the greater ease with which the hydride particle can be transferred to the carbonyl carbon.[30] This may be envisaged as the "B strain" in (VII) leading to a facile H^- separation which leads to virtual non-participation of the aluminocomplex in the stereochemistry of reduction.



(VII)

Using sodium trimethoxyborohydride, the reduction is considered to involve the participation of the hydride ion in conjunction with the boron complex (see later).

Borohydride in various solvents:—The actual effective size of the reducing species using a borohydride reagent will depend upon the nature of the solvent since chemical interaction between the reagent and various solvents is known. The equivalence of the effective size of the borohydride reagent in water, tetrahydrofuran and *iso*propanol is indicated by the similar isomeric ratios obtained on reduction of tropinone in these solvents (Table 1, nos. 6, 16 and 19).

In the aqueous methanol system, increase in the methanol content gave an increase

[28] H. C. Brown, E. J. Mead and P. A. Tierney, *J. Amer. Chem. Soc.* **79**, 5400 (1957).
[29] W. G. Dauben, E. J. Blanz, Jr., J. Jiu and R. A. Micheli, *J. Amer. Chem. Soc.* **78**, 3752 (1956).
[30] H. C. Brown, E. J. Mead and C. J. Sharp, *J. Amer. Chem. Soc.* **78**, 3616 (1956).

VOL. 6 1959

in the tropine content of the product (Table 1, nos. 10, 11, 12 and 13) indicating the participation of a larger reducing species, presumably the methoxyborohydrides, since $NaBH_4 + CH_3OH \rightarrow NaBH_3(OCH_3) + CH_3OH \rightarrow NaBH_2(OCH_3)_2 + CH_3OH \rightarrow NaBH(OCH_3)_3 + CH_3OH \rightarrow NaB(OCH_3)_4$,[25] this pattern may be influenced by disproportionation. The products of reduction will depend on the ratio of the various borohydride species present and their relative rates of reaction. Increase in the methanol content will yield more of the larger, more reactive trimethoxyborohydride (the participation of the tropoxy species in the reaction must play a less important role than in the case of $LiAlH_4$ reductions). The use of borohydride in ethanol might be expected to give an even larger ethoxyborohydride reducing species, but the contraindication of the results is easily explained by the slower rate of reaction between $NaBH_4$ and ethanol[31] and therefore the greater participation of the smaller BH_4^- species. This trend is further indicated in the case of *n*-butanol (Table 1, nos. 13, 14 and 15). The similarity of the isomeric ratios obtained using borohydride in water, tetrahydrofuran and *iso*propanol already noted is not unexpected since Brown *et al.*[30,31] have shown that $NaBH_4$ reacts with lower straight chain but not branched chain alcohols such as *iso*propanol and *t*-butanol.

Sodium trimethoxyborohydride in methanol might be expected to give isomeric ratios similar to those of borohydride in methanol; the discrepancy in the results (Table 1, nos. 13 and 22) is explicable in terms of the different contributions of two reactions, one the irreversible reaction of the borohydride with methanol, the other the reversible disproportionation of methoxyborohydrides as follows:

$$2\,NaBH(OCH_3)_3 \rightleftharpoons NaBH_2(OCH_3)_2 + NaB(OCH_3)_4.$$

The different results obtained using $NaBH(OCH_3)_3$ in methanol and in water indicates the increased contribution of large species in the former solvent, methanol reacting with the BH_4^- produced by disproportionation to give the larger substituted borohydrides (Table 1, nos. 20 and 22).

The reducing capacity of the borohydride ion is markedly affected by the metal ion present,[32] e.g. $NaBH_4$ reduces an ester slowly but $LiBH_4$ rapidly. Hardy and Wicker[13] found that KBH_4 in aqueous ethanol gave 41 per cent but $NaBH_4$ in aqueous methanol gave 61 per cent of the more stable isomer upon reduction of 2-methyl*cyclo*hexanone. However, changes in solvent composition rather than the cation component may have effected this result. Reduction of tropinone with $NaBH_4$ and KBH_4 in water gave results similar to those obtained using $LiBH_4$ in tetrahydrofuran (Table 1, nos. 6, 17 and 19); non-participation of the cation in the course of the reaction is therefore indicated.

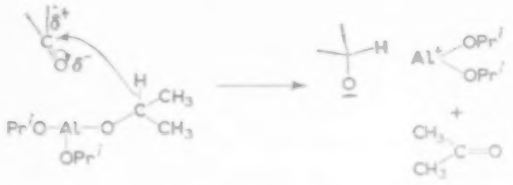
In order to establish whether nascent hydrogen plays a significant part in the reduction, an inverse addition to the ketone of a solution of sodium borohydride in water, in which visible evolution of hydrogen had ceased, was carried out, this gave an isomeric mixture similar to that obtained on direct addition (Table 1, nos. 7 and 9).

Aluminium iso*propoxide in* iso*propanol*. Cyclic intermediates in aluminium alkoxide reductions have been postulated.[33–36] Woodward[33] considered the hydride

[31] H. C. Brown, E. J. Mead and B. C. Subba Rao, *J. Amer. Chem. Soc.* **77**, 6209 (1955).
[32] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **78**, 2582 (1956).
[33] R. B. Woodward, N. C. Wendler and F. J. Brutschy, *J. Amer. Chem. Soc.* **67**, 1425 (1945).
[34] W. von E. Doering and T. C. Aschner, *J. Amer. Chem. Soc.* **75**, 393 (1953).
[35] L. M. Jackman and J. A. Mills, *Nature, Lond.* **164**, 789 (1949).
[36] L. M. Jackman and A. K. Macbeth, *J. Chem. Soc.* 3252 (1952).

attack on the carbon of the carbonyl group to be the initiating and rate controlling step whereas Jackman *et al.*[35,38] considered an initial complexing of aluminium to the carbonyl oxygen followed by the rate controlling hydride attack on the carbonyl carbon.

Since equilibration involving Na and *n*-pentanol and $Al(OPr^{i(so)})_3$ gave comparable results, and reduction using the latter gave a much higher proportion of tropine than occurs in the equilibrated product, the following reaction in which the bulk effect of the reagent is in evidence in the kinetic control is indicated.



Co-ordination of the lone pair of the tropane nitrogen with aluminium may also facilitate approach from side "a" (see I) and so increase the production of the tropine isomer.

Sodium and alcohol. Recently Hardy and Wicker[13] have questioned whether reduction with sodium in alcohol always leads to production of the equilibrium mixture and have emphasised the importance of temperature in this reaction. Reduction of tropinone using Na in ethanol/toluene or in *iso*butanol/toluene under differing conditions of temperature gave results which were identical with those obtained on equilibration (Table 1, nos. 25, 26, 27 and 28, cf. 35 and 36).

EXPERIMENTAL

Materials. Distillation of commercial tropinone gave a pure sample which softened at 38° and melted at 41–43°. (Found: equiv. 140·8; Calc. for $C_8H_{13}ON$: 139·1) (Willstatter[37] quotes m.p. 42°). Commercially available tropine had m.p. 42–49° (Found: equiv. 142; Calc. for $C_8H_{15}ON$: 141) and this was shown by infra-red analysis to contain 94 per cent. tropine and 6 per cent. ψ-tropine (tropinone was absent). Recrystallisation of the commercial tropine from benzene gave a sample m.p. 64° (Orechoff and Konowalowa[38] quote m.p. 63–64°) and this was used where necessary. Pseudotropine m.p. 109–110° was obtained by reduction of tropinone according to the method of Nickon and Fieser[41] (Willstatter *et al.*[37] quote m.p. 108°).

General. Organic layers, before evaporation to give the reduction product, were dried over anhydrous sodium sulphate. The reduction product was stored in a vacuum desiccator for at least 48 hr before assay. Equivalent weights were determined by titration with 0·02 N perchloric acid in glacial acetic acid with Oracet Blue B as indicator.[39] The percentage of total base (calculated as amino-alcohol equivalent weight 141·1) was calculated from the found equivalent weight.

Reduction with lithium aluminium hydride

(i) *Ether as solvent.* A solution of tropinone (5·0 g) in ether (20 cc) was added dropwise over a period of 0·5 hr to a suspension of $LiAlH_4$ (0·70 g) in ether (100 cc) and the mixture refluxed for 5 hr. After cooling, the mixture was decomposed with damp ether, and the ether solution separated. The inorganic residue was washed with ether, then refluxed with absolute alcohol, the combined organic layers filtered and evaporated to yield 4·93 g of a reduction product (2). In a similar reduction which was decomposed and extracted immediately after the addition of ketone, 4·52 g of a reduction product

[37] R. Willstatter, *Ber. Dtsch. Chem. Ges.* **29**, 936 (1896).
[38] A. Orechoff and R. Konowalowa, *Ber. Dtsch. Chem. Ges.* **67**, 1153 (1934).
[39] A. H. Beckett and E. H. Tinley, *Titration in Non-Aqueous Solvents* (2nd Ed.). British Drug Houses, Poole.

(1) was obtained. Tropinone (2·00 g) was reduced with $LiAlH_4$ (2·18 g) in ether (100 cc) refluxing for 3 hr, yielding 1·80 g reduction product (3). Reduction of tropinone (2·00 g) with an assayed solution of $LiAlH_4$ in ether (35·5 cc containing 0·0039 g $LiAlH_4$ in 1 ml)[40] yielded 1·80 g reduction product (4).

(ii) *Tetrahydrofuran as solvent*. The first reduction was repeated using tropinone (2·00 g) and lithium aluminium hydride (0·28 g) in tetrahydrofuran (100 cc) to give 1·96 g of reduction product (5).

Reduction with sodium borohydride

(i) *Water as solvent*. Sodium borohydride (0·40 g) was added to a solution of tropinone (5·00 g) in water (50 cc) when immediate effervescence occurred. The solution was allowed to stand for 24 hr at 20°, and was then extracted with chloroform (10 × 50 cc) which on evaporation gave 4·60 g of reduction product (7). The reduction was repeated (a) at 20° for 2 hr and (b) by refluxing for 48 hr when 4·79 g and 4·20 g respectively of reduction products were obtained (6 and 8). In a reverse addition, a solution of sodium borohydride (0·20 g) in 10 per cent aqueous sodium hydroxide solution (25 cc) was allowed to stand until all effervescence had ceased. A solution of tropinone (2·00 g) in water (25 cc) was added and after standing the solution at 20° for 2 hr it was extracted with chloroform, which on evaporation gave 1·81 g of reduction product (9).

(ii) *Aqueous methanol as solvent*. Sodium borohydride (0·80 g) was added to a solution of tropinone (2·00 g) in 25 per cent aqueous methanol (50 cc) when immediate effervescence occurred. After standing the solution at 20° for 6 hr the bulk of the solvent was evaporated, water (10 cc) added and the mixture extracted with chloroform, which on evaporation gave 1·84 g of reduction product (10). The reduction was repeated by refluxing for 6 hr using as solvent (a) 95 per cent aqueous methanol and (b) absolute methanol when 1·87 g and 1·95 g respectively of reduction products (12 and 13) were obtained. Tropinone was reduced by a modification of the method of Dauben *et al.*[11] A solution of sodium borohydride (0·66 g) in a mixture of 1 part water and 5 parts methanol (12 cc) was added to a solution of tropinone (2·50 g) in methanol (5 cc). After standing the solution at 20° for 16 hr the bulk of the solvent was removed under reduced pressure, water (10 cc) added and the mixture extracted with chloroform, which on evaporation gave 2·39 g of reduction product (11).

(iii) *Alcohols as solvent*. The reduction using absolute methanol was repeated using (a) absolute ethanol, (b) *n*-butanol and (c) *iso*propanol (2 hr reflux) as solvents when 1·89 g, 1·99 g and 1·97 g, respectively of reduction products 14, 15 and 16 were obtained.

Reduction with potassium borohydride

(i) *Water as solvent*. Potassium borohydride (0·26 g) was added to a solution of tropinone (2·00 g) in water (50 cc) when immediate effervescence occurred. After standing the solution for 24 hr at 20° it was extracted with chloroform, which on evaporation gave 1·90 g of reduction product (17).

(ii) *Methanol as solvent*. The reduction using sodium borohydride in methanol was repeated using potassium borohydride (1·17 g) when 1·87 g of reduction product was obtained (18).

Reduction with lithium borohydride

(i) *Tetrahydrofuran as solvent*. A solution of tropinone (2·00 g) in tetrahydrofuran (50 cc) was added dropwise during 0·25 hr to a stirred suspension of lithium borohydride (0·16 g) in tetrahydrofuran (50 cc) and the mixture refluxed for 5 hr. Water (10 cc) was added and the tetrahydrofuran separated. The aqueous layer was extracted with chloroform, the combined organic layer evaporated, the residue dissolved in dry ether, which after filtering and evaporation gave 1·90 g of reduction product (19).

Reduction with sodium trimethoxyborohydride

(i) *Water as solvent*. Sodium trimethoxyborohydride (0·9 g) was added to a solution of tropinone (2·00 g) in water (50 cc) and the mixture allowed to stand at 20° for 2 hr after which it was extracted with chloroform, which on evaporation gave 1·94 g of reduction product (20). In a similar experiment the mixture was refluxed for 48 hr yielding 1·99 g reduction product (21).

(ii) *Methanol as solvent*. Sodium trimethoxyborohydride (2·00 g) was added to a solution of tropinone (2·00 g) in methanol (50 cc) and the mixture refluxed for 6 hr. The bulk of the solvent was

[40] H. Felkin, *Bull. Soc. Chim. Fr.* 347 (1951).
[41] A. Nickon and L. F. Fieser, *J. Amer. Chem. Soc.* **74**, 5566 (1952)

removed under reduced pressure, and water (10 cc) added. Extraction of the aqueous phase with chloroform gave on evaporation 1·82 g of reduction produce (22).

Reduction with aluminium isopropoxide

Tropinone (5·00 g) was added to a solution of aluminium *iso*propoxide (14·0 g) in absolute *iso*propanol (100 cc) and the solution heated in a water bath at 96° for 2·5 hr. The bulk of the solvent was removed under reduced pressure, and the residue acidified with acetic acid. On making alkaline with concentrated ammonium hydroxide solution, extraction with chloroform gave 4·62 g of reduction product (23). The reduction was repeated using tropinone (2·50 g), aluminium *iso*propoxide (7·0 g) and *iso*propanol (50 cc) and heating for 1·5 hr (when reduction was shown to be complete). The complex was decomposed with hydrochloric acid, made alkaline with sodium hydroxide solution, extracted with chloroform which on evaporation gave 2·39 g of reduction product (24).

Reduction with sodium–alcohol

A solution of tropinone (20·0 g) in a mixture of toluene (20 cc) and absolute ethanol (16 cc) was added over a period of 0·3 hr to sodium (6·5 g) in toluene (50 cc). The solution was refluxed for 3 hr, cooled, water (30 cc) added and the aqueous layer separated and extracted with toluene. A red oil was separated form the combined toluene layer and discarded, and the toluene evaporated to give 19·4 g of a reduction product (25). In a similar reduction using *iso*butanol in place of ethanol, 19·1 g of a reduction product (26) was obtained.

In a low temperature reduction, tropinone (2·06 g) in a mixture of toluene (20 cc) and *iso*butanol (3 cc) was added with stirring to an ice-cooled suspension of sodium (0·65 g) in toluene (20 cc) over 1 hr. The solution was stirred overnight, water (10 cc) added and extracted as above to give 1·83 g of a reduction product (27). In a similar reduction tropinone (2·02 g) yielded 1·80 g reduction product (28).

Equilibration of tropines

(i) *Sodium*/n-*pentanol*. The following general procedure was adopted. A solution of the alcohol (2 g) in *n*-pentanol (20 cc) was added to sodium *n*-pentoxide prepared from sodium (4 g) and *n*-pentanol (20 cc) and the mixture refluxed. After cooling and decomposing with water, dilute hydrochloric acid was added and the aqueous layer separated. This was made alkaline with dilute sodium hydroxide solution and extracted with chloroform, which on evaporation gave the equilibrium alcohol mixture (34–36).

(ii) *Aluminium* iso*propoxide*. The following general procedure was adopted. The alcohol (1·5 g) was added to a solution of aluminium *iso*propoxide (2·16 g) in *iso*-propanol (50 cc), acetone (0·5 cc) added, and the mixture refluxed. On completion of the reaction, acetic acid was added, the mixture made alkaline with concentrated ammonium hydroxide solution and extracted with chloroform, which on evaporation gave the equilibrium alcohol mixture (29–33).

(iii) *Sodium* iso*butoxide*. A solution of tropine (1 g) in a mixture of *iso*butanol (1·5 cc) and toluene (10 cc) was added, with stirring, to an ice-cooled suspension of sodium (0·33 g) in toluene (10 cc) over 1 hr. The solution was stirred overnight and water (5 cc) added, and the aqueous layer separated and extracted with chloroform. The combined organic layers were evaporated to give 0·91 g equilibrium alcohol mixture (37).

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VOL.
6
1959

ANTHRAQUINONE AND ANTHRONE SERIES—XXIII*

THE NON-IDENTITY OF 1:3:8-TRIHYDROXY-2-HYDROXYMETHYL-ANTHRAQUINONE WITH VERSICOLORIN AND A SYNTHESIS OF DAMNACANTHOL AND DAMNACANTHAL

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(*Received* 9 *December* 1958)

Abstrac:—1:3:8-Trihydroxy-2-hydroxymethylanthraquinone has been synthesised by hydroxymethylation of 1:3:8-trihydroxyanthraquinone and shown to be different from versicolorin, the colouring matter isolated by Hatsuda and Kuyama from *Aspergillus versicolor*. Damnacanthol and damnacanthal, the colouring matters of the roots of *Damnacanthus major* and *D. indicus* have been synthesised by a new route.

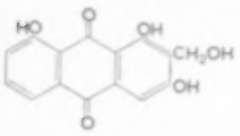
FROM the mycelium of *Aspergillus versicolor* (Vuillemin) Tiraboschi, cultured on a malt extract medium containing glucose and peptone, Hatsuda and Kuyama[1] isolated two colouring matters, versicolorin, yellow-orange needles, m.p. 282°, and sterigmatocystin, yellow needles, m.p. 243°. Hatsuda *et al.*[2] ascribed to sterigmatocystin the molecular formula $C_{15}H_{12}O_5$ and a structure derived from xanthhydrol. This pigment was isolated later from the same organism by Davies *et al.*[3] and by Birkinshaw and Hammady.[4] The latter authors found the molecular formula of sterigmatocystin to be $C_{18}H_{12}O_6$, which excluded both the molecular and structural formulae proposed by Hatsuda. Birkinshaw and Hammady also obtained a second optically active pigment which crystallised from chloroform in long orange needles, m.p. 233–234°. Although colour reactions and ultra-violet absorption spectra indicated it to be a polyhydroxyanthraquinone, the H : C ratio was too high. The colouring matter was not identical with versicolorin which had a different melting point and for which no optical activity was reported.

Versicolorin has been isolated from *A. versicolor* only by the Japanese workers, and they have assigned the molecular formula $C_{15}H_{10}O_6$ and the structure I or II. Evidence for the hydroxyanthraquinone structure was a purple colour in aqueous sodium hydroxide, which disappeared on heating with zinc dust and was restored by air oxidation. With alcoholic magnesium acetate versicolorin gave an orange solution, indicating that two hydroxyl groups were probably located *meta* to each other.[5] The formation of a tetra-acetate and a trimethyl ether by heating with dimethyl sulphate, potassium carbonate and acetone showed the presence of one alcoholic and three phenolic hydroxyl groups. By analogy with other fungal anthraquinones two hydroxyls were placed in 1:8-positions, the three phenolic hydroxyls therefore being

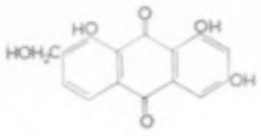
* Part XXII: *Tetrahedron* **3**, 62 (1958).

[1] Y. Hatsuda and S. Kuyama, *J. Agr. Chem. Soc. Japan* **28**, 989 (1954).
[2] Y. Hatsuda, S. Kuyama and N. Terashima, *J. Agr. Chem. Soc. Japan* **28**, 992, 998 (1954); **29**, 11 (1955).
[3] J. E. Davies, J. C. Roberts and S. C. Wallwork, *Chem. & Ind.* 178 (1956).
[4] J. H. Birkinshaw and I. M. M. Hammady, *Biochem. J.* **65**, 162 (1957).
[5] S. Shibata, M. Takido and O. Tanaka, *J. Amer. Chem. Soc.* **72**, 2789 (1950).

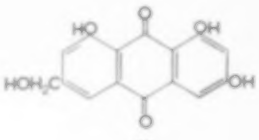
in the 1:3:8-positions. The 6-position for the hydroxymethyl group was ruled out, since versicolorin would then be identical with citreorosein (III: ω-hydroxyemodin). On the assumption that the hydroxymethyl group was in a β-position, based on the fact that no naturally occurring anthraquinone colouring matter with a hydroxymethyl group in an α-position has so far been encountered, it followed that versicolorin was constituted as I or II.



I



II



III

1:3:8-Trihydroxy-2-hydroxymethylanthraquinone (I) has now been synthesised by an unambiguous method, and several of its properties are different from those described for versicolorin, a sample of which was kindly supplied by Professor Hatsuda. Versicolorin therefore does not have the structure I. We have shown

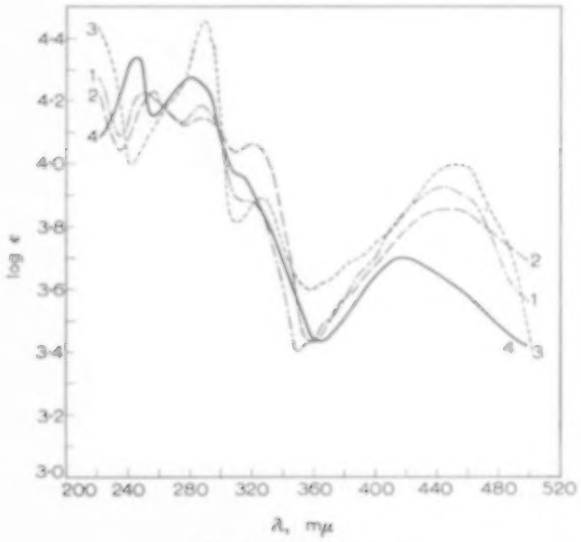


FIG. 1. Solvent—ethanol.

Absorption spectra of:
1. — · — · — 1:3:8-Trihydroxyanthraquinone
2. — — — 1:3:8-Trihydroxy-2-hydroxymethylanthraquinone
3. – – – – Versicolorin
4. ——— Lucidin (1:3-dihydroxy-2-hydroxymethylanthraquinone)

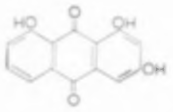
earlier that lucidin (2-hydroxymethylxanthopurpurin) can be readily synthesised by the condensation of xanthopurpurin (1:3-dihydroxyanthraquinone) with formaldehyde and sodium hydroxide solution.[6] Likewise, hydroxymethylation of 1:3:8-trihydroxyanthraquinone (IV) gave an excellent yield of I, which darkens and decomposes at 295°; the m.p. quoted for versicolorin is 282°. The tetra-acetates of I and versicolorin melt at 205° and 225° respectively.

[6] N. R. Ayyangar and K. Venkataraman, *J. Sci. Ind. Res.* **B15**, 359 (1956).

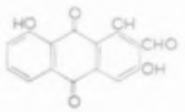
VOL. 6 1959

Versicolorin and the synthetic compound I differ in their absorption spectra in the ultra-violet and visible regions (Fig. 1; lucidin and 1:3:8-trihydroxyanthraquinone are included for comparison). The infra-red spectrum of I (KBr pellet) shows absorption bands at 3436 cm^{-1} (alcoholic and β-hydroxyl groups, which are not distinguishable), 1670 cm^{-1} (unchelated carbonyl) and 1617 cm^{-1} (chelated carbonyl). In the region above 1600 cm^{-1} the following maxima have been recorded[7] for lucidin (1:3-dihydroxy-2-hydroxymethylanthraquinone): 3448, 3367, 1667 and 1621 cm^{-1}. Versicolorin shows absorption bands at 3330 cm^{-1}, 1673 cm^{-1} (very weak band seen as an inflexion or shoulder), and 1620 cm^{-1}. Reviewing Hatsuda's work on versicolorin, Thomson[8] has stated that "as there appears to be only one carbonyl band in the infra-red spectrum these (structures I and II) must be accepted with reserve," but there are two carbonyl bands in the infra-red spectrum of the sample of versicolorin sent to us by Professor Hatsuda. When the infra-red spectra were determined in Nujol, the chelated carbonyl band of both I and versicolorin was overlapped by the phenyl band and a strong absorption band was observed around 1604–1606 cm^{-1}. This type of overlapping of the phenyl and chelated carbonyl bands has been observed in the infra-red spectra of 1:5- and 1:8-dihydroxyanthraquinones determined by the Nujol mull technique.[9] The possibility of versicolorin having the structure II cannot be eliminated on the available evidence, and the synthesis of II is in progress.

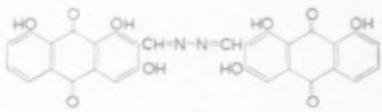
Oxidation of I with manganese dioxide in boiling benzene gave the corresponding aldehyde V, which is of interest on account of the occurrence of other hydroxyanthraquinone aldehydes, damnacanthal (see below) and fallacinal,[10] in nature. Two molecules of the aldehyde (V) reacted with hydrazine to give the compound (VI), establishing that the aldehyde group in V occupies a β-position and that IV therefore had undergone hydroxymethylation in the 2-position yielding I. If IV had undergone hydroxymethylation in the 4-position, the corresponding aldehyde would have reacted only with one molecule of hydrazine to form a pyridazine derivative.



IV



V

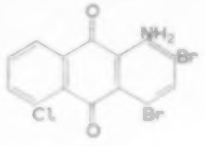


VI

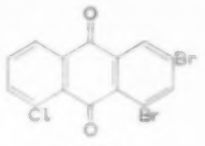
A synthesis of 1:3:8-trihydroxyanthraquinone (IV) starting from 1-amino-6:8-dichloroanthraquinone was reported earlier,[11] but the following route is more convenient. Bromination of 1-amino-5-chloroanthraquinone gave 1-amino-2:4-dibromo-5-chloroanthraquinone (VII). Deamination of VII by diazotization and boiling with ethanol gave the trihalogenoanthraquinone (VIII), which was converted to 1:3:8-trimethoxyanthraquinone by refluxing with sodium methoxide and copper oxide in methanol. The replacement of both the α- and β-halogens by methoxyl groups was facilitated by the use of copper oxide. When VIII was heated with calcium hydroxide and copper bronze under pressure, only the α-halogens were replaced by hydroxyl

[7] L. H. Briggs and G. A. Nicholls, *J. Chem. Soc.* 3068 (1953).
[8] R. H. Thomson, *Naturally Occurring Quinones* p. 206. Butterworths, London (1957).
[9] O. Tanaka, *Pharm. Bull. Japan* **6**, 18 (1958).
[10] T. Murakami, *Pharm. Bull. Japan* **4**, 298 (1956).
[11] N. Parkash and K. Venkataraman. *J. Sci. Ind. Res.* **B13**, 825 (1954).

groups. Demethylation of the trimethyl ether by means of aluminium chloride–sodium chloride at 145–150° then yielded 1:3:8-trihydroxyanthraquinone (IV).

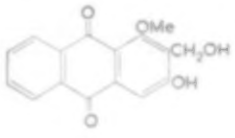


VII

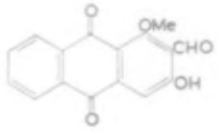


VIII

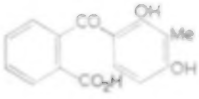
Nonomura[12] isolated two colouring matters, damnacanthol (IX) and damnacanthal (X), from the roots of the Japanese *Rubiaceae Damnacanthus major* Sieb and Zucc., *D. major* Sieb and Zucc. var. *parvifolius* Koidz., and *D. indicus* Gaertner fil. var. *microphyllus* Makino. He indicated the close similarity between damnacanthal (X) and the compound $C_{16}H_{10}O_5$, m.p. 208°, isolated by Perkin and Hummel[13] from *Morinda umbellata* Linn. While the present work was in progress, Hirose[14] reported the synthesis of IX and X, starting from the very difficultly accessible resorcinol



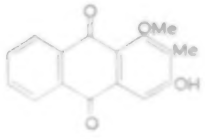
IX



X



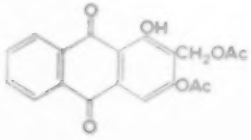
XI



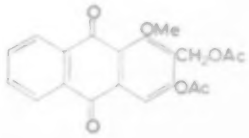
XII

derivative (XI). The keto-acid (XI) was cyclized to rubiadin, from which the 1-methyl ether (XII) was prepared and submitted to the action of N-bromosuccinimide, following our route for the synthesis of lucidin from rubiadin.[15] As mentioned earlier, lucidin has become readily available by the direct hydroxymethylation of xanthopurpurin, and the preparation of damnacanthol (IX) and damnacanthal (X) from lucidin is now described.

Lucidin-2:3-diacetate (XIII) was prepared by heating a solution of lucidin, boroacetic anhydride and acetic anhydride, and treating the diboroacetate thus



XIII



XIV

[12] S. Nonomura, *J. Pharm. Soc. Japan* **75**, 219, 222, 225 (1955).
[13] A. G. Perkin and J. J. Hummel, *J. Chem. Soc.* **65**, 854 (1894).
[14] Y. Hirose, *J. Pharm. Soc. Japan* **76**, 1448 (1956).
[15] B. S. Joshi, N. Parkash and K. Venkataraman, *J. Sci. Ind. Res.* **B14**, 87 (1955).

formed with water; XIII could also be obtained by acetylating lucidin with acetic anhydride and potassium acetate at 15–20°. Methylation of XIII with diazomethane to 1-methoxy-2-acetoxymethyl-3-acetoxyanthraquinone (XIV) and subsequent hydrolysis with methanolic potassium hydroxide gave damnacanthol (IX), m.p. 295° (dec). The alcohol (IX) on oxidation with manganese dioxide in boiling benzene gave X, m.p. 211°, undepressed on admixture with a sample of natural damnacanthal kindly supplied by Professor Nonomura. The identity of the synthetic compound (X) and natural damnacanthal was also shown by the ultra-violet and infra-red spectra.

VOL. 6 1959

EXPERIMENTAL

1-*Amino*-2:4-*dibromo*-5-*chloroanthraquinone* (VII). To a stirred mixture of 1-amino-5-chloroanthraquinone (20 g) and glacial acetic acid (800 ml) at 100°, bromine (20 ml) in glacial acetic acid (40 ml) was added drop by drop in 2 hr. Agitation was continued at 100° for 5 hr, and the dark red product was then collected, washed with 2 per cent sodium bisulphite solution and water, and dried (26 g). Crystallisation from chlorobenzene gave dark red needles, m.p. 250° (Found: C, 40·5; H, 1·9; N, 3·3; Cl, 8·7; Br, 39·0. $C_{14}H_6O_2Br_2ClN$ requires: C, 40·5; H, 1·5; N, 3·4; Cl, 8·4; Br, 38·6%).

1:3-*Dibromo*-8-*chloroanthraquinone* (VIII). 1-Amino-2:4-dibromo-5-chloroanthraquinone (25 g) was dissolved in conc H_2SO_4 (250 ml), cooled in an ice-bath to 5°, and diazotised with sodium nitrite (20 g) in conc H_2SO_4 (100 ml) for 1 hr. Glacial acetic acid (50 ml) was added, and after 15 min, the mixture was poured over crushed ice (1 kg). The solution of the diazonium salt was added to ethanol (1 l.) and the mixture was gradually heated to the boil and then refluxed for 30 min. The greyish yellow product was collected, washed free of acid and dried (22 g). Crystallisation from glacial acetic acid gave greyish yellow needles, m.p. 245° (Found: C, 41·6; H, 1·2. $C_{14}H_5O_2Br_2Cl$ requires: C, 42·0; H, 1·3%).

3-*Bromo*-1:8-*dihydroxyanthraquinone*. A mixture of 1:3-dibromo-8-chloroanthraquinone (VIII; 5 g), calcium hydroxide (30 g), copper bronze (2 g) and water (100 ml) was heated in a rocking autoclave at 230° and 27 atmospheres pressure for 24 hr. The violet calcium salt was acidified with 5% HCl, the brown product collected, washed, and extracted with 5% NaOH, and the extract acidified. The precipitate was collected, washed free of acid and dried (2·6 g). On extraction with petroleum ether, an orange yellow product (2 g) was obtained, which on crystallisation from glacial acetic acid gave orange-yellow needles m.p. 210° (Found: C, 53·2; H, 2·1; Br, 25·1. $C_{14}H_7O_4Br$ requires: C, 52·7; H, 2·2; Br, 25·1%).

The *diacetyl* derivative crystallised from glacial acetic acid in pale yellow needles, m.p. 192° (Found: C, 53·7; H, 2·4; Br, 20·2. $C_{18}H_{11}O_6Br$ requires: C, 53·6; H, 2·7; Br, 19·8%).

1:3:8-*Trimethoxyanthraquinone*. 1:3-Dibromo-8-chloroanthraquinone (3 g) and copper oxide (1 g) were refluxed for 24 hr with sodium methoxide solution prepared by reacting sodium (7·5 g) with dry methanol (150 ml). The mixture was then poured into water (500 ml), and the yellow product was collected, washed and dried (1·95 g). It crystallised from ethanol in yellow platelets, m.p. 196°.[11] (Found: C, 68·8; H, 4·8; OMe, 29·9. $C_{17}H_{14}O_5$ requires: C, 68·5; H, 4·8; OMe, 31·2%).

1:3:8-*Trihydroxyanthraquinone* (IV). 1:3:8-Trimethoxyanthraquinone (1·7 g) was added to a melt of anhydrous aluminium chloride (8 g) and sodium chloride (1·5 g) at 145–150°. The mixture was stirred at 150° for 5 min and then poured into 5% HCl (150 ml). The brown-red precipitate was coagulated by heating for a few min, collected (1·5 g), and crystallised from ethyl acetate; the brown plates melted at 287°.[11] (Found: C, 65·5; H, 3·1. $C_{14}H_8O_5$ requires: C, 65·6; H, 3·1%). The substance dissolves in conc H_2SO_4 with a reddish orange colour and gives a red solution in aqueous caustic soda and sodium carbonate. These properties are in agreement with those described.[11] The infra-red spectrum (KBr pellet) shows maxima at 3330, 1670, 1617, 1582, 1480, 1454, 1416, 1368, 1338, 1280, 1230, 1163, 1056, 1020, 973, 913, 881, 863, 831, 821, 807, 778, 759, 741 and 724 cm^{-1}.

1:3:8-*Trihydroxy*-2-*hydroxymethylanthraquinone* (I). A solution of 1:3:8-trihydroxyanthraquinone (1·5 g) in 5% NaOH (20 ml) was cooled to 20–25°, and treated with formalin (37–40%; 0·6 ml) under stirring. After 30 min agitation at 20–25°, the mixture was allowed to stand for 16 hr, then acidified, and the golden yellow precipitate collected, washed and dried (1·5 g). The product, which was very sparingly soluble in ethyl acetate and ethanol, crystallised from dioxan in orange yellow

microscopic needles, darkening and decomposing above 295°. (Found: C, 62·8; H, 3·8. $C_{15}H_{10}O_6$ requires: C, 62·9; H, 3·7%). The substance gives a red solution in sodium carbonate and sodium hydroxide solutions and a brown solution in H_2SO_4. Versicolorin gives a violet solution in sodium carbonate and sodium hydroxide solutions and a bright violet solution in H_2SO_4. The infra-red spectrum shows maxima at 3436, 2940, 1670, 1617, 1572, 1480, 1454, 1416, 1368, 1338, 1309, 1280, 1254, 1218, 1196, 1163, 1039, 996, 974, 916, 897, 877, 859, 838, 807, 793, 765 and 730 cm^{-1}. Versicolorin shows maxima at 3330, 2940, 1670, 1620, 1582, 1484, 1449, 1382, 1313, 1284, 1236, 1218, 1182, 1163, 1064, 1044, 1030, 996, 970, 940, 904, 874, 857, 824, 781, 761, 742 and 723 cm^{-1}.

The *tetracetyl* derivative, prepared in the usual manner by means of acetic anhydride and pyridine, crystallised from ethanol in pale yellow needles, m.p. 205° (Found: C, 60·4; H, 4·0. $C_{23}H_{18}O_{10}$ requires: C, 60·8; H, 4·0%).

1:3:8-*Trimethoxy*-2-*hydroxymethylanthraquinone*. A mixture of 1:3:8-trihydroxy-2-hydroxymethylanthraquinone (0·14 g), anhydrous potassium carbonate (3 g), dimethyl sulphate (0·25 ml), and acetone (100 ml) was refluxed on a water-bath for 24 hr. After removal of the acetone and dilution of the mixture with water, a yellow product was obtained, which crystallised from ethanol in shining yellow needles, m.p. 220° (Found: C, 65·9; H, 4·7. $C_{18}H_{16}O_6$ requires: C, 65·9; H, 4·9%).

1:3:8-*Trihydroxyanthraquinone*-2-*aldehyde* (V). 1:3:8-Trihydroxy-2-hydroxymethylanthraquinone (IV, 0·4 g) and activated manganese dioxide[15] (0·8 g) were refluxed with benzene (150 ml) for 16 hr. The mixture was filtered hot, and the manganese dioxide residue washed several times with hot benzene. Evaporation of the solvent and crystallisation of the residue from glacial acetic acid gave brownish yellow needles (0·25 g), m.p. 223° (Found: C, 63·4; H, 3·0. $C_{15}H_8O_6$ requires: C, 63·4; H, 2·8%). The aldehyde dissolves in warm sodium hydroxide solution with a red-violet colour, and in conc H_2SO_4 with an orange-red colour. The *azine* (VI) was prepared by treating a warm solution of V (0·01 g) in glacial acetic acid (5 ml) with excess of hydrazine hydrate solution. Immediately a flocculent yellow crystalline precipitate separated. Crystallisation from nitrobenzene gave yellow needles, m.p. >360°. (Found: N, 5·0. $C_{30}H_{16}O_{10}N_2$ requires: N, 5·0%).

Lucidin-2:3-*diacetate* (XIII). (a) Lucidin[6] (2 g) was refluxed with a mixture of boroacetic anhydride (5 g) and acetic anhydride (25 ml) for 5 min. The crystalline diboroacetate which separated was filtered, washed with ice-cold acetic anhydride containing boroacetic anhydride and finally with ether. The diboroacetate was suspended in water (100 ml) for 12 hr at room temp. The product (2 g) gave on crystallisation from ethanol yellow needles, m.p. 152° (Found: C, 64·4; H, 3·9. $C_{19}H_{14}O_7$ requires: C, 64·2; H, 3·9%). An ethanolic solution of XIII gives a brown colour with alcoholic ferric chloride.

(b) A mixture of lucidin (1·5 g), acetic anhydride (10 ml) and potassium acetate (1 g) was agitated at 15–20° for one hr and kept overnight. It was then poured into ice-cold water (100 ml) and the product (1·6 g) collected. Crystallisation from ethanol gave yellow needles, m.p. 152°, identical with the diacetate obtained by method (a).

3-*Acetoxy*-2-*acetoxymethyl*-1-*methoxyanthraquinone* (XIV). To a solution of lucidin-2:3-diacetate (3 g) in tetrachloroethane (40 ml) excess of ethereal diazomethane was added under stirring. After 48 hr excess of diazomethane was destroyed by acetic acid, ether distilled off, and tetrachloroethane removed by steam distillation; the residue crystallised from ethanol in yellow needles (1·5 g), m.p. 156–157° (Found: C, 65·3; H, 4·5; OMe, 8·1. $C_{20}H_{16}O_7$ requires: C, 65·2; H, 4·3; OMe, 8·4%).

Lucidin-1-*methylether* (*Damnacanthol;* IX). A solution of XIV (1·5 g) in 5% methanolic potassium hydroxide (50 ml) was maintained at 25° for 24 hr. Acidification with acetic acid gave a bright yellow crystalline product (0·75 g) which crystallised from ethanol in yellow needles, m.p. 295° (with darkening) (Found: C, 67·5; H, 4·2; OMe, 11·1. $C_{16}H_{12}O_5$ requires: C, 67·5; H, 4·2; OMe, 10·9%).

3-*Hydroxy*-1-*methoxyanthraquinone*-2-*aldehyde* (*Damnacanthal;* X). Lucidin-1-methyl ether (0·5 g) was refluxed with manganese dioxide[16] and benzene (40 ml) for 24 hr, and the solution filtered hot. The manganese dioxide residue was washed several times with hot benzene. After removal of the benzene, the residue (0·3 g) crystallised from ethanol in orange-yellow needles, m.p. 211°, undepressed on admixture with a sample of natural damnacanthal kindly supplied by Prof. Nonomura (Found C, 68·4; H, 3·6. $C_{16}H_{10}O_5$ requires: C, 68·1; H, 3·6%). The infra-red spectra of damnacanthal and the compound (X) in carbon tetrachloride show maxima at 2935, 1965, 1876, 1754, 1670, 1610, 1570, 1510, 1468, 1382, 1354, 1270, 1220, 1194, 1064, 1030 and 982 cm^{-1}. In the ultra-violet and

[16] M. Harfenist, A. Bavley and W. A. Lazier, *J. Org. Chem.* **19**, 1608 (1954).

visible regions both damnacanthal and X exhibit the following maxima: 2500, 2810, 3800 and 6150 Å; log ε_{max} 4·40, 4·37, 3·60 and 3·20 respectively.

The 2:4-*dinitrophenylhydrazone* of X crystallised from nitrobenzene in golden yellow needles, m.p. 300° (Found: N, 12·3. $C_{21}H_{12}O_8N_4$ requires: N, 12·1%).

Acknowledgements—We are indebted to Professor Hatsuda for a sample of versicolorin, to Professor Nonomura for a sample of damnacanthal, to the Council of Scientific and Industrial Research for the award of a fellowship to one of us (N. R. A.), to Dr. G. D. Shah and Mr. V. S. Pansare for the microanalyses recorded in the paper, and to Dr. (Mrs.) S. Dasgupta for the infra-red spectra.

VOL.
6
1959

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STEREOCHEMISTRY OF THE PRIMARY CARBON—X

STEREOCHEMICAL CONFIGURATIONS OF SOME OPTICALLY ACTIVE DEUTERIUM COMPOUNDS*

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Chemistry Department, University of California, Berkeley, California

Abstract—The *iso*bornyloxymagnesium halide reduction of the appropriate deutero-aldehyde yields benzyl-α-*d* alcohol and 1-butanol-1-*d* having the same configuration and about the same level of optical purity. Arguments are presented that these alcohols are close to optical purity. The relative configurations of each alcohol were established by converting each to 1-phenylbutane-1-*d* using reactions of known or presumed stereochemistry. The rotations and configurations of 18 optically active deuterium compounds are summarized.

WE have previously described the preparation of optically active 1-butanol-1-*d*[1,2] and benzyl-α-*d* alcohol[3] by the partially asymmetric reduction of the corresponding deutero-aldehydes with the Grignard reagent of an optically active secondary alcohol. In this paper we derive the relative and absolute configurations of these alcohols and that of some other optically active deuterium compounds using considerations of stereochemistry based on reaction mechanisms. The alcohols were stereochemically interrelated by converting both to 1-phenylbutane-1-*d*.

Both alcohols have been prepared using the *iso*bornyl system as the reducing agent. The use of this system is especially convenient since it can be prepared readily from camphor which is available as the optically pure dextrorotatory enantiomer. Lithium aluminum hydride reduction yields (—) *iso*borneol contaminated with about 10 per cent of borneol.[4] Vavon and Antonini[5] have shown that *iso*bornyloxymagnesium bromide will reduce phenyloxalic acid to yield mandelic acid of 15 per cent optical purity; borneol was inert to these conditions. Since borneol reacts so much more slowly than *iso*borneol, its presence in the reducing agent is not objectionable.

The reduction of benzaldehyde-*d* with *iso*bornyloxymagnesium bromide gave benzyl-α-*d* alcohol having $[\alpha]_D$ −0·715°.‡ This alcohol is used as an internal standard; in subsequent reactions diluted material was often used but the rotations are readily corrected to correspond to the level of optical purity of the standard benzyl-α-*d* alcohol.

* This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

† This paper was taken in part from the Ph.D. Dissertations of J. R. Wolfe, Jr. (1957) and W. D. Schaeffer (1956), University of California.

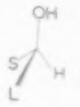
‡ This rotation is about 10 per cent higher than that previously determined,[3] because of the use of benzaldehyde-*d* of higher deuterium content. The deutero-aldehyde was prepared by the Stephen reduction of benzonitrile with stannous chloride and deuterium chloride. Slotta and Kethur[6] have reported that completely anhydrous stannous chloride will not dissolve in ether. The water present in the original preparation explains the isolation of isotopically impure benzaldehyde-*d*.[3] In the present case anhydrous stannous chloride was prepared and some deuterium oxide was added prior to the Stephen reduction. The resulting benzaldehyde-*d* had only a very weak triplet at 3·6 μ indicative of aldehydic hydrogen; the benzyl-α-*d* alcohol prepared from this aldehyde had 0·98 atoms of deuterium per molecule.

[1] A. Streitwieser, Jr., *J. Amer. Chem. Soc.* **75**, 5017 (1953).
[2] A. Streitwieser, Jr. and W. D. Schaeffer, *J. Amer. Chem. Soc.* **78**, 5597 (1956).
[3] A. Streitwieser, Jr. and J. R. Wolfe, Jr., *J. Amer. Chem. Soc.* **79**, 903 (1957).
[4] D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.* **72**, 5743 (1950).
[5] G. Vavon and A. Antonini, *C. R. Acad. Sci., Paris* **232**, 1120 (1951).
[6] K. H. Slotta and R. Kethur, *Ber.* **71**, 335 (1938).

The mechanism of reduction by halomagnesium alkoxides has been proposed to involve a quasi six membered ring.[7,8] Hence, our reductions are directly analogous to the elegant work of Doering and Young[9] on the partially asymmetric reductions of ketones with aluminum alkoxides. The absolute configuration of (+) camphor is I.* Hence, (—) *iso*borneol which is formed on reduction is II. This configuration can be represented as III in which the small methylene group, S, is at the rear and the large quaternary carbon group, L, is in front. In the reduction of a deutero-aldehyde

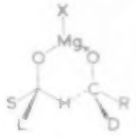
I

II



III

by a halomagnesium alkoxide from III the cyclic mechanism[7,8] can proceed by each of two transition states. The more stable depicted in IV involves steric interactions between the small group, S, and the large group, R, and between the large group, L, and the small deuterium. The alternative structure involves steric oppositions between the large L group and the large R group and is of higher energy.[9] The deutero-alcohol which results from IV has the configuration in V.



IV

V

Since this reduction with benzaldehyde-*d* yields (—) benzyl-α-*d* alcohol, the (+) alcohol has the configuration VI. It is interesting that (+) α-phenethyl alcohol has the same configuration[15] with a methyl group replacing the deuterium.

VI

VII

VIII

* The stereochemical interrelationships among the terpenes as interpreted by Hückel[10] and their relationship with the sugars by the "quasi-racemate" method of Fredga[11] has been summarized by Birch.[12] Fredga's assignments have been confirmed by the elegant chemical conversions of Freudenberg[13] and of Noyce and Denney.[14]

[7] M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances* p. 160. Prentice-Hall, New York (1954).
[8] H. S. Mosher and E. LaCombe, *J. Amer. Chem. Soc.* **72**, 3994 (1950).
[9] W. E. Doering and R. W. Young, *J. Amer. Chem. Soc.* **72**, 631 (1950); L. M. Jackson, J. A. Mills and J. S. Shannon, *Ibid.* **72**, 4814 (1950).
[10] W. Hückel, *J. prakt. Chem.* **157**, 225 (1941).
[11] A. Fredga, *The Svedberg Memorial Volume* p. 261. Almquist and Wiksells Boktryckeri, Upsala (1944); *Acta Chem. Scand.* **1**, 361 (1947).
[12] A. J. Birch, *Ann. Rep. Prog. Chem.* **47**, 192 (1950).
[13] K. Freudenberg, *Angew. Chem.* **65**, 259 (1953).
[14] D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.* **76**, 768 (1954).
[15] J. A. Mills and W. Klyne in W. Klyne's *Progress in Stereochemistry* Vol. I, p. 187. Butterworths Scientific Publications, London (1954).

The reduction of undeuterated butyraldehyde with deuterated *iso*borneol yields deuterated butyl alcohol having α_D +0·154 ± 0·104° (*l*4) and 0·55 deuterium atoms per molecule. Thus the 1-butanol-1-*d* produced in this reduction has $[\alpha]_D$ +0·172 ± 0·004. By the same argument considered above, the (+) alcohol has the configuration in VII. Benzyl-α-*d* alcohol and 1-butanol-1-*d* of the same sign of rotation have the same configuration according to this reasoning. The same conclusion with respect to the absolute configuration of 1-butanol-1-*d* was reported by Levy, Loewus and Vennesland[16] based on application of the same reasoning to the production of (−) 1-butanol-1-*d* by the reduction of butyraldehyde with (+) 2-octanol-2-*d*.[1] This agreement may be taken as additional evidence for the correctness of the relative configurations assigned to *iso*borneol and 2-octanol.

The tosylate prepared from benzyl-α-*d* alcohol having α_D^{25} −0·983 ± 0·004° (*l*4), with tosyl chloride and pyridine was treated with sodioacetoacetic ester in benzene to yield ethyl benzyl-α-*d*-acetoacetate, α_D^{25} −0·263 ± 0·005° (*l*2). The formation of the tosylate ester does not affect the asymmetric center; the subsequent reaction of the tosylate is undoubtedly a direct displacement reaction with complete inversion of configuration;* Hence, the (−) substituted acetoacetic ester is represented by VIII (R = $CH(COOC_2H_5)COCH_3$). Hydrolysis of ethyl benzyl-α-*d*-acetoacetate, α_D^{25} −0·145° ± 0·004° (*l*2), gave 4-phenyl-2-butanone-4-*d*, α_D^{26} −0·158 ± 0·008° (*l*2); Clemmensen reduction gave 1-phenylbutane-1-*d*, α_D^{26} −0·179 ± 0·005° (*l*1·5). Since these reactions take place away from the asymmetric center, the (−) ketone and (−) hydrocarbon are represented by VIII (R = CH_2COCH_3 and $CH_2CH_2CH_3$, respectively). By application of the appropriate corrections the rotation of 1-phenylbutane-1-*d* which corresponds to the standard alcohol is $[\alpha]_D$ −0·78 ± 0·04°.

Thermal decomposition of the chlorosulfite prepared from 1-butanol-1-*d*, α_D^{25} −0·142 ± 0·004° (*l*4), gave 1-chlorobutane-1-*d*, α_D^{25} + 0·147 ± 0·004° (*l*2), with 91 ± 2 per cent inversion of configuration.[17] The stereochemistry of this reaction was established by a comparison of the optical activity of the 1-butyl-1-*d* acetate prepared by esterification of the starting alcohol with that observed by the direct displacement of the butyl chloride with tetramethylammonium acetate in acetone. Hence the configuration of the (+) chloride is IX (R = Cl).

1-Phenylbutane-1-*d* was prepared from the chloride by reaction with excess phenyl lithium in benzene. The reaction of phenyl lithium with *n*-butyl chloride in butyl ether has been shown to yield *n*-butylbenzene in high yield and to follow second order kinetics.[18] Hence this reaction is very probably of the direct displacement type of inversion of configuration.† Because of the solubility of lithium chloride in ethers and the consequent possibility of partial racemization of 1-chlorobutane-1-*d* by the

* The reaction of benzyl-α-*d* tosylate with alcoholic sodium ethoxide has been demonstrated to go with complete inversion of configuration (J. R. Wolfe, Jr., unpublished results).

† Several analogous cases are known involving the reactions of sodium alkyls with *sec*-alkyl halides.[19–21] The reactions of benzylsodium with *sec*-butyl chloride[22] and of allylsodium with α-phenethyl chloride[22] apparently involve little, if any, racemization. Corresponding reactions of a primary chloride would be expected to involve still less racemization.

[16] H. R. Levy, F. A. Loewus and B. Vennesland, *J. Amer. Chem. Soc.* **79,** 2949 (1957).
[17] A. Streitwieser, Jr. and W. D. Schaeffer, *J. Amer. Chem. Soc.* **79,** 379 (1957).
[18] S. J. Cristol, J. W. Ragsdale and J. S. Meeks, *J. Amer. Chem. Soc.* **73,** 810 (1951).
[19] R. L. Letsinger, *J. Amer. Chem. Soc.* **70,** 406 (1948).
[20] R. L. Letsinger and J. G. Traynham, *J. Amer. Chem. Soc.* **72,** 849 (1950).
[21] S. E. Ulrich, F. H. Gentes, J. F. Lane and E. S. Wallis, *J. Amer. Chem. Soc.* **72,** 5127 (1950).
[22] R. L. Letsinger, L. G. Maury and R. L. Burwell, Jr., *J. Amer. Chem. Soc.* **73,** 2373 (1951).
[23] R. L. Burwell, Jr., A. D. Shields and H. Hart, *J. Amer. Chem. Soc.* **76,** 908 (1954).

chloride ion liberated in the reaction, the displacement with phenyl lithium was carried out in benzene solution, in which lithium chloride is insoluble. There is the possibility that the excess phenyl lithium would cause partial racemization of the product 1-phenylbutane-1-*d* by a metalation reaction. This possibility was eliminated

IX

by a comparison of the rotation of 1-phenylbutane-1-*d* isolated after about 80 per cent reaction, α_D^{25} $-0{\cdot}142 \pm 0{\cdot}01°$ (*l*1) with that isolated after complete reaction, α_D^{25} $-0{\cdot}148 \pm {\cdot}01°$ (*l*1). Hence, the (+) hydrocarbon has the configuration IX ($R = C_6H_5$)—the (−) hydrocarbon is VIII ($R = C_3H_7$). This configuration is identical with that assigned from the benzyl-α-*d* alcohol approach and confirms the relative configurations deduced above for the alcohols.

By comparing the rotations of the 1-phenylbutane-1-*d*'s obtained from the two alcohols and working back in a straight-forward manner, the rotation of 1-butanol-1-*d* of the same optical purity as benzyl-α-*d* alcohol is $[\alpha]_D^{25}$ $0{\cdot}185 \pm 0{\cdot}018°$. The 1-butanol-1-*d* produced by the reduction of butyraldehyde-*d* with 2-octanol had only about one-fourth this rotation; however, that obtained from the *iso*borneol reduction had $0{\cdot}93 \pm 0{\cdot}09$ times this rotation (*vide supra*); i.e., *iso*borneol reduces benzaldehyde and butyraldehyde with about equal stereospecificity although the stereospecificity involves a differential steric effect with a phenyl group on the one and with a *n*-propyl group on the other. In other asymmetric reactions, a phenyl group is usually considered to have a larger effective bulk than a *n*-alkyl group;[24] consequently, we would expect the reduction of benzaldehyde to be rather more stereospecific than the reduction of butyraldehyde. The approximate equality of the stereospecificity strongly suggests that both reductions with *iso*borneol are close to 100 per cent stereospecific; i.e., the rotation of the standard benzyl-α-*d* alcohol (*vide supra*) is rather close to the rotation of optically pure alcohol.

This conclusion about the near optical purity of the alcohols obtained by the *iso*borneol reduction receives further support by the following arguments. In an elegant series of experiments, Loewus, Westheimer and Vennesland[25] demonstrated that ethanol-l-*d* produced by the enzymatic reduction of acetaldehyde-*d* by yeast alcohol dehydrogenase is optically pure. Enough of this alcohol was recently isolated for a determination of the rotation, $[\alpha]_D$ $-0{\cdot}28 \pm 0{\cdot}03°$.[16] It is a reasonable assumption that the molecular rotation of ethanol-l-*d* and butanol-l-*d* be closely comparable.* If they were identical, optically pure butanol-l-*d* would have $[\alpha]_D$ 0·18°. The close correspondence with the observed value is probably fortuitous but demonstrates that our alcohols are probably not far from optical purity.

* In the series of methyl *n*-alkyl carbinols the molecular rotations change smoothly from 10·3° for 2-butanol to 14·5° for 2-tridecanol; the variation from 2-octanol to 2-tridecanol is less than 2°.[26] To the extent that the variations in rotation are due to a comparison of the mass of the alkyl group with the methyl group, substitution of deuterium for methyl should cause the molecular rotations to effectively level off much earlier in the series. *Added in proof:* The analogy may be inappropriate; preliminary experiments suggest that ethanol-1-*d* and butanol-1-*d* of the same configuration have opposite rotations.

[24] D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).
[25] F. A. Loewus, F. H. Westheimer and B. Vennesland, *J. Amer. Chem. Soc.* **75**, 5018 (1953).
[26] J. H. Pickard and J. Kenyon, *J. Chem. Soc.* **99**, 45 (1911).

A similar argument applies to 1-phenylethane-1-*d* which was originally prepared by Eliel[27] as one of the first compounds known with demonstrated optical activity due to hydrogen-deuterium asymmetry. The optically pure hydrocarbon has a rotation of about $[\alpha]_D$ −0·73 ± 0·06°;* the molecular rotation, $[M]_D$ +0·68 ± ·06° is only slightly higher than the molecular rotation, $[M]_D$ −0·58 ± ·04°, of the 1-phenylbutane-1-*d* obtained from benzyl-α-*d* alcohol and suggests again the near

TABLE 1. ROTATIONS AND CONFIGURATIONS OF OPTICALLY ACTIVE DEUTERIUM COMPOUNDS

R_1	R_2	$[\alpha]_D$[a]	Reference
C_6H_5	OH	+0·715 ± 0·002°	b
C_6H_5	Br	+0·60 ± 0·20°	3
C_6H_5	$OCOCH_3$	+0·172 ± 0·004°	3
C_6H_5	$OCOC_6H_4COOH(o)$	−0·219 ± 0·005°[c]	3
C_6H_5	NH_2	+1·025 ± 0·015°	28
C_6H_5	$CH(COOEt)COCH_3$	−0·39 ± 0·01°	b
C_6H_5	CH_2COCH_3	−0·44 ± 0·03°	b
C_6H_5	OC_2H_5	+0·096 ± 0·003°	28
C_6H_5	$CH_2CH_2CH_3$	−0·78 ± 0·04°	b
C_6H_5	CH_3	−0·73 ± 0·06°	d
$CH_2CH_2CH_3$	OH	+0·185 ± 0·018°	
$CH_2CH_2CH_3$	Cl	+0·39 ± 0·03°	17
$CH_2CH_2CH_3$	$OCOCH_3$	−0·48 ± 0·04°	17, 29
$CH_2CH_2CH_3$	$OSO_2C_6H_4NO_2(p)$	−0·136 ± 0·038°[e]	30
$CH_2CH_2CH_3$	$OSO_2C_6H_4Br(p)$	−0·078 ± 0·016°	29
$CH_2CH_2CH_3$	$OCOC_6H_4COOH(o)$	−0·38 ± 0·05°[e]	29, 31
CH_3	OH	+0·28 ± 0·03°	17
CH_3	CH_2CH_3	−0·56 ± 0·01°	32

[a] Rotations are given for the undiluted liquids (neat) unless stated otherwise; except for 1-phenylethane-1-*d* and ethanol-1-*d*, the rotations refer to compounds of the same relative optical purity. The two exceptions are optically pure compounds.
[b] This paper.
[c] Acetone, c 20.
[d] See text.
[e] Acetone, c 28.

* Eliel[27] prepared 1-phenylethane-1-*d*, $[\alpha]_D^{25}$ −0·30°, by the reaction of α-phenethyl chloride, $[\alpha]_D^{25}$ −49·2°, with lithium aluminum deuteride. Optically pure α-phenethyl chloride has $[\alpha]_D$ 117 ± 8°;[29] hence, if the reduction is considered to be a direct displacement reaction with complete inversion of configuration, optically pure 1-phenylethane-1-*d* has $[\alpha]_D^{25}$ 0·70 ± ·05°. In a repetition of this experiment in these laboratories, α-phenethyl chloride, $[\alpha]_D^{28}$ +59·9° gave 1-phenylethane-1-*d*, $[\alpha]_D^{26}$ +0·390°, whence for optically pure material the rotation is $[\alpha]_D^{26}$ 0·76 ± ·05° (L. Reif, unpublished results).

[27] E. C. Eliel, *J. Amer. Chem. Soc.* **71**, 3970 (1949).
[28] J. R. Wolfe, Jr., unpublished results.
[29] A. Streitwieser, Jr., *J. Amer. Chem. Soc.* **77**, 1117 (1955).
[30] A. Streitwieser, Jr. and W. D. Schaeffer, *J. Amer. Chem. Soc.* **79**, 6233 (1957).
[31] S. Andreades, unpublished results.
[32] G. K. Helmkamp, C. D. Joel and H. Sharman, *J. Org. Chem.* **21**, 844 (1956).

optical purity of our preparations. It is interesting to note that 1-phenylethane-1-*d* and 1-phenylbutane-1-*d* of the same rotation have the same configuration.

The rotations and configurations of a number of optically active deuterium compounds are summarized in Table 1. The rotations of the compounds derived from the benzyl or butyl systems are given for materials of the same optical purity as the standard benzyl-α-*d* alcohol; by the arguments presented above these rotations all correspond to materials of near optical purity.

EXPERIMENTAL

Benzyl-α-d *alcohol*. The benzaldehyde-*d* used in this preparation was synthesized as before[3] with the following modifications: Anhydrous stannous chloride was prepared by the method of Stephen[33] and was stored over concentrated sulfuric acid under reduced pressure for several days. After the addition of 1·5% by weight of deuterium oxide the material was used for the Stephen reduction of benzonitrile.[3] The deuterium chloride required for this reduction was prepared by the reaction of benzoyl chloride with deuterium oxide. The product benzaldehyde-*d* was isolated and purified as the sodium bisulfite addition compound. In the best of several runs 34% of the addition compound was obtained using 3 moles of benzonitrile, 2·73 moles of deuterium oxide and 3·5 moles of stannous chloride in 1200 ml of dry ether. The reduction to optically active benzyl-α-*d* alcohol was accomplished as previously described.[3] The product had α_D^{30} −3·006 ± 0·004° (*l*4), α_{5463}^{30} −3·669 ± 0·004° (*l*4), n_D^{20} 1·5383 and d_4^{25} 1·0509. The density of the alcohol corresponds to a deuterium content of 0·98 deuterium atoms per molecule.[34]

Benzyl-α-d p-*toluenesulfonate*. The method used was essentially that of Edgell and Parts[35] for the synthesis of methyl tosylate. In a dry system 20 g of dry pyridine and 10 ml of benzyl-α-*d* alcohol were cooled to −40°. After the addition of 28·6 g of tosyl chloride, 80 g of dry pyridine was dropped in over a period of 1·5 hr and the mixture was stirred for an additional 1·5 hr while the system was maintained at −40°. The mixture was poured into 2 liters of ice water and extracted with ether. The washed and dried ether solution was cooled to 0° and a large excess of dry pentane or hexane was added to induce crystallization. The filtered crystals were maintained in vacuum at 0° to remove remaining solvent and were stored at dry ice temp until used. The yield was 50–55%.

Ethyl benzyl-α-d-*acetoacetate*: To the sodioacetoacetic ester prepared from 32·6 g of redistilled ethyl acetoacetate and 5 g of powdered sodium in 300 ml of dry benzene, was added at room temp 200 ml of a benzene solution containing the benzyl-α-*d* tosylate prepared from 10 ml of benzyl-α-*d* alcohol having α_D^{25} −0·983 ± 0·004°, α_{5463}^{25} −1·216 ± 0·013° (*l*4). After stirring for 24 hr, the mixture was poured into ice and dilute sulfuric acid. The washed and dried organic phase was distilled yielding 10 g (45% yield) of ethyl benzyl-α-*d*-acetoacetate, b.p. 148–152° (6 mm), having α_D^{25} −0·263 ± 0·005° (*l*2).

4-*Phenyl*-2-*butanone*-4-d: Ethyl benzyl-α-*d*-acetoacetate, α_D^{28} −0·145° ± 0·004° (*l*2), was stirred with 5% aqueous sodium hydroxide for several hours. After extraction with ether the aqueous solution was acidified with sulfuric acid and was steam distilled. The distillate was extracted with ether. Distillation of the washed and dried ether extract afforded the product ketone, b.p. 115–118° (12–13 mm), α_D^{26} −0·158 ± 0·008° (*l*2).

1-*Phenylbutane*-1-d *from* 4-*phenyl*-2-*butanone*-4-d: The ketone (3·6 ml) prepared above was refluxed for 10 hr with dilute hydrochloric acid and zinc amalgam prepared from 60 g of mossy zinc and 8 g of mercuric chloride. Additional hydrochloric acid was added at intervals. The cooled reaction mixture was extracted with pentane. Distillation of the dried extract gave 2·3 ml of colorless hydrocarbon, b.p. 106–107° (75 mm), α_D^{27} −0·188 ± 0·004° (*l*1·5). After purification of the product by chromatography on silica gel followed by treatment with acidic potassium permanganate, the redistilled material had α_D^{26} −0·179 ± 0·005° (*l*1·5).

1-*Phenylbutane*-1-d *from* 1-*chlorobutane*-1-d: In an atmosphere of nitrogen 100 ml of a benzene solution ·83 M in phenyllithium and 4·82 g of optically active 1-chlorobutane-1-*d*, α_D^{25} +0·147 ± 0·004°

[33] A. J. Vogel, *Practical Organic Chemistry* p. 193. Longmans, Green, London (1948).
[34] A. McLean and R. Adams, *J. Amer. Chem. Soc.* **58**, 804 (1936).
[35] W. F. Edgell and L. Parts, *J. Amer. Chem. Soc.* **77**, 4899 (1955).

(*l*2), was refluxed. Periodically, 1 ml aliquots were withdrawn and titrated to yield the second order rate constants summarized in Table 2. After 24 hr (about 80% reaction) two-thirds of the reaction mixture was poured into dilute hydrochloric acid. The separated organic phase was dried and distilled to yield 1·1 ml of material, b.p. 82–87° (35 mm). The infrared spectrum showed the presence of considerable phenolic material, hence the product was washed with dilute sodium hydroxide and redistilled to yield 0·25 ml of 1-phenylbutane-1-*d*, b.p. 180–185°, α_D^{25} −0·148 ± 0·01° (*l*1).

TABLE 2. KINETICS OF DISPLACEMENT OF 1-CHLOROBUTANE-1-*d* BY PHENYL LITHIUM

Time (sec)	Titer	$k_2 \times 10^3$ (l. mole/sec)
0	0·790	—
2520	0·750	4·4
11900	0·635	2·8
18000	0·610	3·7
61200	0·454	3·4
∞	0·275	—
	Av.	3·6 ± 0·5

The remaining one-third of the reaction mixture was refluxed an additional 24 hr and after cooling was poured into dilute sodium hydroxide. The dried organic phase was distilled to yield 0·3 ml of hydrocarbon, b.p. 78–82° (30 mm), α_D^{25} −0·142 ± 0·01° (*l*1). The infrared spectra of the two samples were identical.

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DIENON-PHENOL-UMLAGERUNG VON CHINOLEN—II*

BEITRAG ZUR KLÄRUNG DES REAKTIONSMECHANISMUS

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(*Received* 26 *December* 1958)

Zusammenfassung—Es werden Umlagerungen von *o*- und *p*-Chinolacetaten und von *p*-Chinolen unter den Bedingungen der Thieleschen Reaktion beschrieben. Zur Klärung des Reaktionsmechanismus wurden auch Umlagerungen in Diacetylsulfid durchgeführt.

Der Dualismus im Reaktionsverhalten zwischen *p*-Chinolen und *p*-Chinolacetaten wird ausführlich diskutiert.

Die Ergebnisse der Säureeinwirkung auf *p*-Toluchinol und dessen Acetat sind mit unseren Vorstellungen über den Ablauf der anderen hier behandelten Reaktionen im Einklang.

Abstract—Rearrangements of *o*- and *p*-quinol-acetates and of *p*-quinols under conditions of the Thiele-reaction are described. To investigate the mechanism of these reactions rearrangements have also been carried out in diacetyl-sulphide.

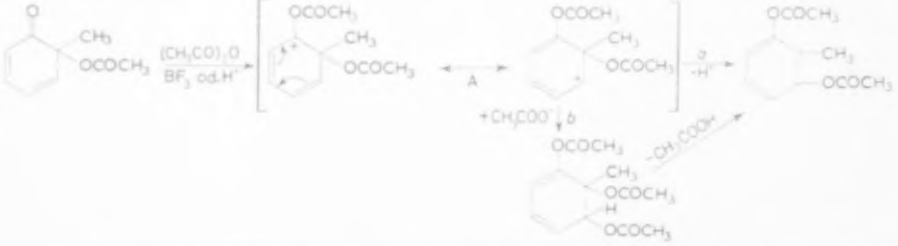
The differences between the reactions of *p*-quinols and *p*-quinol-acetates are being discussed in some detail.

The results of action of acids upon *p*-toluquinol and its acetate are in accordance with our conceptions on the course of other reactions mentioned in this paper.

1. *Mechanismus der Dienon-Phenol-Umlagerung bei Chinolacetaten*

WITKOP hat als erster in einer vorläufigen Notiz,[1] der Jahre später die ausführliche Arbeit gefolgt ist,[2] u.a. Versuche über die "Thiele"-Reaktion an *p*-Chinolacetaten und einen Mechanismus hiezu veröffentlicht. Die Ergebnisse, die wir[3] bei dieser Reaktion an *o*-Chinolacetaten erhalten hatten, liessen sich in gleicher Weise deuten.

Das Wesen der Reaktion, die als Dienon-Phenol-Umlagerung zu bezeichnen ist, lässt sich am Beispiel des 2-Methyl-*o*-chinolacetates folgendermassen schematisch darstellen:



Aus dem durch Addition einer Antibase (=Lewis-Säure), z.B. des Acetyliumions

* Als I. Mitteilung zählen wir die früher als Untersuchungen über Chinole IV bezeichnete Arbeit *Mh. Chem.* **85**, 637 (1954).

† Herrn Prof. P. Karrer zum 70. Geburtstag in Verehrung gewidmet.

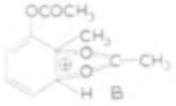
[1] B. Witkop und S. Goodwin, *Experientia* **8**, 377 (1952).
[2] S. Goodwin und B. Witkop, *J. Amer. Chem. Soc.* **79**, 179 (1957).
[3] F. Wessely und W. Metlesics, *Mh. Chem.* **85**, 637 (1954).

CH_3CO^+, an das Carbonyl-Sauerstoffatom entstandenen mesomeren Kation A kann das aromatische Reaktionsprodukt auf zwei Arten entstehen:

(1) *Reaktion a:* Durch eine interne Wanderung des Acetatrestes des Chinolacetates an das positivierte C-Atom und Abspaltung eines Protons,

(2) *Reaktion b:* Der Acetatrest wird aus dem Lösungsmittel Acetanhydrid aufgenommen. Der aromatische Zustand würde in diesem Fall durch Abspaltung von Essigsäure hergestellt werden.

Witkop gibt der ersten Möglichkeit den Vorzug, die er entsprechend den vor allem von Winstein[4] und Ingold[5] entwickelten Vorstellungen mit einem "verbrückten Kation" B formuliert:



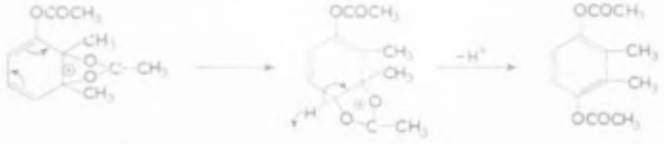
B

Witkop stützt seine Formulierung auf das experimentelle Ergebnis, dass bei der Einwirkung von BF_3-Ätherat auf 4-Methyl-*p*-chinolacetat das Kresorcin-2-acetat entsteht.

Wir haben versucht, auf einem anderen Weg die Möglichkeit einer externen Addition eines Acetations entsprechend b zu prüfen. In einer früheren Arbeit hat einer von uns gezeigt,[6] dass Diacetylsulfid bei der Einwirkung auf Hydroxyverbindungen und Chinone sich analog wie das Acetanhydrid verhält, d.h. unter geeigneten Bedingungen in Form der Ionen CH_3CO^+ und CH_3COS^- reagiert.

Lässt man nun Diacetylsulfid bei Gegenwart von BF_3 auf 2-Methyl-*o*-chinolacetat und 4-Methyl-*p*-chinolacetat einwirken, so erhält man kein Thiophenol, sondern nur die gleichen Acetoxyverbindungen in praktisch der gleichen Ausbeute wie bei der Reaktion mit Acetanhydrid. Damit ist also ein weiterer experimenteller Hinweis dafür erbracht, dass der zweite Acetoxylrest nicht aus dem Lösungsmittel Acetanhydrid aufgenommen wird. Es gilt also für diese beiden Chinolacetate nicht der Weg b, denn sonst wäre die Bildung eines Thiophenols zu erwarten, vorausgesetzt, dass die externe Addition eines Acetoxylrestes nicht rascher erfolgt als die eines Thioacetations (CH_3COS^-).

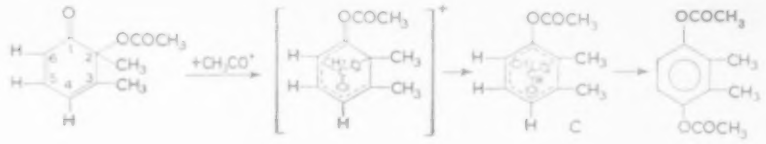
Etwas anders als bei den beiden oben angeführten Chinolacetaten liegen aber schon die Verhältnisse beim 2:3-Dimethyl-*o*-chinolacetat. Bei der Umlagerung in Acetanhydrid[3] war als Hauptprodukt (85%) 2:3-Dimethylhydrochinondiacetat erhalten worden. Der Acetatrest ist also an das β-ständige C-Atom getreten. Diese 1:3-Wanderung forderte, wenn man die interne Verschiebung des Acetatrestes über ein verbrücktes Kation vom Typus B erklären wollte, eine zweimalige Wiederholung dieses Vorganges:



[4] S. Winstein und R. E. Buckles, *J. Amer. Chem. Soc.* **65**, 613 (1943).
[5] C. K. Ingold, *Structure and Mechanism in Organic Chemistry*. Cornell Univ. Press, N.Y. (1953).
[6] W. Metlesics, *Mh. Chem.* **88**, 804 (1957).

VOL. 6 1959

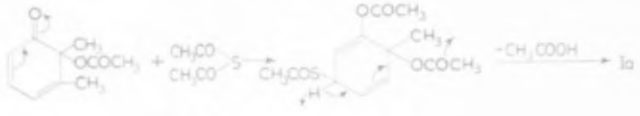
Wie man durch räumliche Betrachtungen erkennen kann, ist diese 1:3-Wanderung auch durch eine "direkte" Übertragung der Acetoxygruppe an das β-C-Atom möglich, so wie es die unten stehende Formulierung verdeutlichen soll. Das Wesentliche ist die Ausbildung eines Übergangszustandes C, in dem die gelockerten, bzw. noch nicht hergestellten Bindungen zwischen den O-Atomen des Acetoxyrestes und den C-Atomen 2 und 4 durch die punktierte Linie symbolisiert sind. Bei der Allylumlagerung ist diese 1:3-Wanderung experimentell bewiesen worden.[7]



Die Herstellung der Bindung mit dem C-Atom 4 ist durch den mit der Abspaltung eines Protons verbundenen Energieabfall zum aromatischen System bedingt.

Wenn die Herstellung dieses Übergangszustandes C eine grössere Aktivierungsenthalpie erfordert als für die Bildung des verbrückten Kations B bei einer 1:2-Wanderung nötig ist, so muss die Reaktion zum Hydrochinondiacetat langsamer erfolgen als die Bildung des 2:6-Diacetoxytoluols aus dem 2-Methyl-*o*-chinolacetat. Tatsächlich haben wir bei der Umlagerung dieses Chinolacetates auch eine geringe Menge Toluhydrochinondiacetat[3] erhalten.

Ferner haben wir gefunden, dass beim 2:3-Dimethyl-*o*-chinolacetat mit Diacetylsulfid neben der internen Acetatwanderung auch eine externe Addition eines CH_3COS^--Ions als Konkurrenzreaktion eintritt, die zur Bildung des Diacetates eines Dimethylhydroxythiophenols (11% Ausbeute) führt. Dies "externe" Additionsreaktion sollte, so wie es bei der Thieleacetylierung von *p*-Chinonen formuliert wird, dem Mechanismus einer 1:4-Addition folgen:



Dem ebenerwähnten Hydroxythiophenoldiacetat müsste also die Formel Ia zukommen. Das wird durch die IR-Untersuchung des freien Hydroxythiophenols bestätigt.

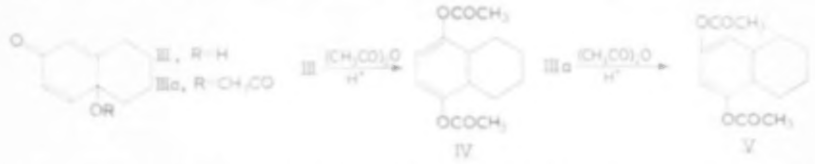
Das IR-Spektrum von Ib zeigt eine starke Bande bei 885 cm^{-1}, die für einen 1:2:3:5-tetrasubstituierten Benzolring spricht. Zum Vergleich zeigt ein nach der

[7] K. Schmid, W. Haegele und H. Schmid, *Experientia* **9**, 414 (1953); E. N. Marrell und R. Terolpishi, *J. Amer. Chem. Soc.* **76**, 6165 (1954).

Vorschrift von Karrer[6] durch Reduktion von 1-Hydroxy-2:3-dimethylbenzolsulfonsäure-(4)[9] hergestelltes Hydroxythiophenol IIb eine Bande bei 795 cm^{-1} entsprechend einem 1:2:3:4-tetrasubstituierten Benzolring. Weder Ib noch IIb zeigt eine intramolekulare Brückenbindung zwischen OH und SH, wie dies bei Monothiobrenzkatechin der Fall ist, woraus folgt, dass Ib kein Thiobrenzkatechinderivat darstellt.

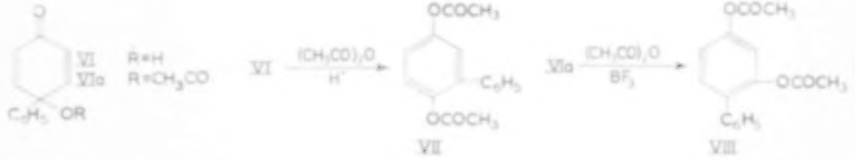
2. *Unterschied im Reaktionsverhalten zwischen* p-*Chinol und* p-*Chinolacetat*

Es ist eine experimentell bewiesene Tatsache, dass die Dienon-Phenol-Umlagerung zu verschiedenen Produkten führt, je nachdem, ob als Ausgangsmaterial die Chinolacetate oder die freien Chinole verwendet werden. So hatte schon Asahina[10] aus dem Tetralylchinol III das 1:2-Diacetoxyderivat IV erhalten, während Witkop[2] aus dem Acetat IIIa unter den gleichen Reaktionsbedingungen das Resorcinderivat V erhielt:*

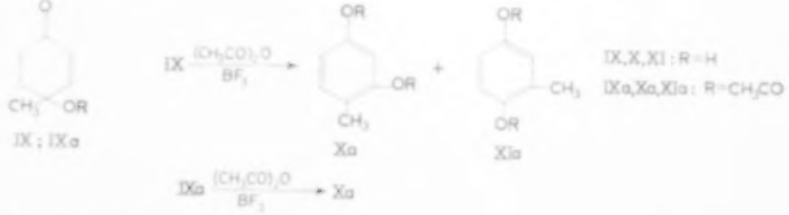


In letzter Zeit haben Gold und Schwenk[11] am 10ξ-Hydroxy-1:4-östradien-3:17-dion und dessen Acetat den gleichen Dualismus beobachtet.

Abe[12] hat aus VI bei der Einwirkung von Acetanhydrid-Schwefelsäure VII erhalten, während wir feststellen konnten, dass aus dem Acetat VIa das Diacetat des Phenylresorcins VIII neben sehr wenig von VII entsteht.



Wir haben ferner nochmals die Einwirkung von Acetanhydrid-BF_3 auf IX bzw. IXa untersucht und dabei festgestellt, dass aus letzterem als einziges Reaktionsprodukt Kresorcindiacetat (Xa) entsteht. Aus IX entstand aber nicht ausschliesslich diese Verbindung (Xa), sondern auch in einer Menge von ca. 20% das Diacetat des Toluhydrochinons (XIa).



* Diese Angaben sind in[3] unrichtig zitiert.

[6] P. Karrer und P. Leiser, *Helv. Chim. Acta* **27**, 678 (1944).
[9] H. Brückner, *Z. Analyt. Chem.* **75**, 289 (1928).
[10] Y. Asahina und T. Momose, *Ber. Dtsch. Chem. Ges.* **71**, 1421 (1938).
[11] A. M. Gold und E. Schwenk, *J. Amer. Chem. Soc.* **80**, 5683 (1958).
[12] Y. Abe, *Bull. Chem. Soc. Japan* **18**, 93 (1943); *Chem. Abstr.* **41**, 4468d (1947).

Schon Witkop hat diesen Dualismus zwischen Chinolen und Chinolacetaten zu erklären versucht und führt die Tatsache, dass einerseits aus III das Diacetylderivat IV entsteht, andererseits aus IX Kresorcindiacetat, auf eine Konkurrenz zweier Reaktionen zurück: "possibly the hydroxyl group of III is more hindered than that of IX and does not become acetylated before the rearrangement."

Es hängt, wenn man die Verhältnisse ausführlich diskutiert, die Art der gebildeten Reaktionsprodukte von der relativen Geschwindigkeit folgender Reaktionen ab:

(1) Acetylierung der freien tertiären OH–Gruppe des Chinols, der die Dienon-Phenol-Umlagerung des Chinolacetates ohne externe Addition einer Acetoxylgruppe folgt,

(2) Dienon-Phenol-Umlagerung des Chinols unter Wanderung des Alkyl- bzw. Arylrestes ohne externe Addition einer Acetoxylgruppe und

(3) Externe Addition der Acetoxylgruppe an

(a) das aus dem Chinol oder

(b) dem Chinolacetat

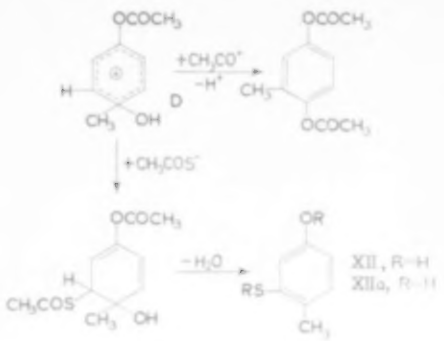
durch Addition von CH_3CO^+ entstehende Kation.

Wenn z.B. bei einem Chinol die Reaktion (1) wesentlich rascher verläuft als die Reaktion (2) und (3), so muss man die gleichen Reaktionsprodukte wie bei der Dienon-Phenol-Umlagerung des entsprechenden Chinolacetates erwarten. Das ist der Fall beim Mesityl-*p*-chinol; an monomeren Reaktionsprodukten konnte nur das Mesorcindiacetat gefunden werden.

Konkurriert jedoch die Geschwindigkeit der Reaktion (2) mit der von (1), so ist mit anderen Reaktionsprodukten zu rechnen, vor allem solchen, bei welchen der Kohlenstoffrest wandert, der an das gleiche C-Atom gebunden ist, wie die tertiäre OH-Gruppe. Da keine Messungen über die Geschwindigkeiten der einzelnen Reaktionen vorliegen, kann man heute nur durch Untersuchung der Reaktionsprodukte jene relativ zu einander abschätzen. Besonders interessierte es, ob die Reaktion (3) überhaupt in Betracht zu ziehen ist.

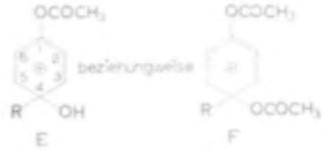
Auch hier haben wir versucht, mit Hilfe des Diacetylsulfides einen Beitrag zur Entscheidung dieser Frage zu liefern: Die Bildung des Kresorcindiacetates Xa aus 4-Methyl-*p*-chinol bei der Dienon-Phenol-Umlagerung in Acetanhydrid könnte damit erklärt werden, dass man primär Acetylierung der tertiären OH-Gruppe zum 4-Methyl-*p*-chinolacetat annimmt (Reaktion 1), das sich, wie die Umlagerung des 4-Methyl-*p*-chinolacetates gezeigt hat, quantativ zu Xa umlagert. Stimmt diese Annahme, dann dürften bei der gleichen Reaktion in Diacetylsulfid keine acetylierten Thiophenole entstehen (s.S. 346). Das ist aber nicht der Fall. Lässt man nämlich auf das 4-Methyl-*p*-chinol IX Diacetylsulfid bei Gegenwart von BF_3 einwirken, so findet man zusätzlich zu X und XI eine Verbindung der Konstitution XIIa.

Die Bildung dieser Verbindung ist nur so zu erklären, dass an das Kation D eine externe Addition einer nukleophilen Partikel entsprechend Reaktion (3a) möglich ist, und dass die Additionsgeschwindigkeit des Anions konkurriert mit der internen Wanderung des Alkylrestes. Man ist also nicht gezwungen, z.B. für die Bildung des Kresorcindiacetates aus *p*-Toluchinol bei der Umlagerung in Acetanhydrid nur eine vorherige Acetylierung der tertiären OH-Gruppe anzunehmen, der dann die interne Wanderung des Acetatrestes folgt, sondern es kann das Kresorcindiacetat auch durch Addition eines externen Acetations an das Kation D entsprechend der Reaktion (3a) entstehen.



Wenn aus einem Chinol bei der Dienon-Phenol-Umlagerung nicht das aus dem entsprechenden Chinolacetat entstehende Umwandlungsprodukt gefunden wird—wie das beim 4-Phenyl-*p*-chinol der Fall ist (s.o.)—, so kann dies dadurch bedingt sein, dass die interne Wanderung des an das C-Atom 4 gebundenen Restes entsprechend der Reaktion 2 sehr rasch gegenüber der externen Addition des Acetations oder der Acetylierung der tertiären OH-Gruppe erfolgt. Dafür spricht, dass beim 4-Phenyl-*p*-chinol ausschliesslich das Hydrochinonderivat gefunden worden ist, beim 4-Methyl-*p*-chinol hingegen nur etwa 20% des Hydrochinons neben dem entsprechenden Resorcinderivat als Hauptprodukt. Es müsste also der Phenylrest bedeutend leichter wandern als der Methylrest

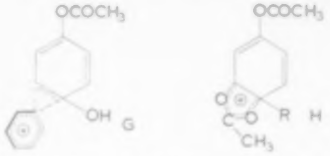
Dieses Verhalten der *p*-Chinole kann folgendermassen verstanden werden: Bei der Dienon-Phenol-Umlagerung handelt es sich in der zweiten Phase der Reaktion um eine nukleophile Substitutionsreaktion der Kationen



In diesen beiden Kationen sind die π-Elektronen unter dem Einfluss der Substituenten (und eventuellen Nachbarn) polarisiert. Die Stelle der geringsten Elektronendichte und damit die Stelle des Eintritts eines Anions wird von der Fähigkeit der Substituenten R, OH und $OCOCH_3$ und ev. von dem nukleophilen Reagens abhängen, an einem C-Atom ein elektrophiles Zentrum entstehen zu lassen. Trägt das C-Atom 4 einen Phenylrest, so kann man auf Grund der Ergebnisse von Ingold[5] bzw. Winstein[4] die Bildung von Kationen des Typus G und damit aus E ($R = C_6H_5$) die Bildung von Phenylhydrochinondiacetat erklären. Die gleichen Überlegungen gelten für die Wanderung der Acetoxylgruppe (F → H). Beim 4-Phenyl-*p*- chinol erfolgt also die Wanderung des Phenylrestes rascher als die Acetylierung der tertiären OH-Gruppe. Aus dem Kation F entsteht quantitativ Kresorcindiacetat, wenn $R = CH_3$ ist, aber neben VIII auch etwas VII bei $R = C_6H_5$, weil die Wanderungsgeschwindigkeit des Phenylrestes wesentlich grösser als die der Methylgruppe im Kation F und der der Acetoxylgruppe vergleichbar ist. Aus dem 4-Methyl-*p*-chinol entsteht in der Hauptmenge Kresorcindiacetat, weil

(1) die Acetylierung der tertiären OH-Gruppe in E ($R = CH_3$) rascher erfolgt als beim 4-Phenyl-*p*-chinol und weil

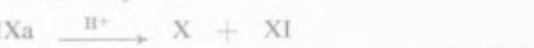
(2) wegen des schwächeren Nachbargruppeneffektes der CH_3-Gruppe[13] die Ausbildung eines verbrückten Kations wesentlich langsamer erfolgen wird als bei der Phenylgruppe.



Über die Dienon-Phenol-Umlagerung der *o*-Chinole, die ein aus den bisherigen Versuchsergebnissen nicht erklärbares Verhalten zeigen, wird in einer gesonderten Arbeit berichtet werden.

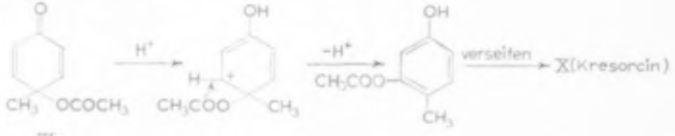
3. *Dienon-Phenol-Umlagerung unter Säurekatalyse*

p-Chinole und ihre Acetate ergeben auch bei der Einwirkung von Säuren verschiedene Reaktionsprodukte. Die von uns erhaltenen Ergebnisse entsprechen den oben entwickelten Vorstellungen über die Umlagerung der *p*-chinoliden Verbindungen. Behandelt man nämlich 4-Methyl-*p*-chinolacetat IXa mit 5proz. methanolischer Schwefelsäure, so erhält man neben dem Hauptprodukt Kresorcin (X) Toluhydrochinon XI in kleiner Menge, während aus dem freien Chinol IX reines Toluhydrochinon XI entsteht.

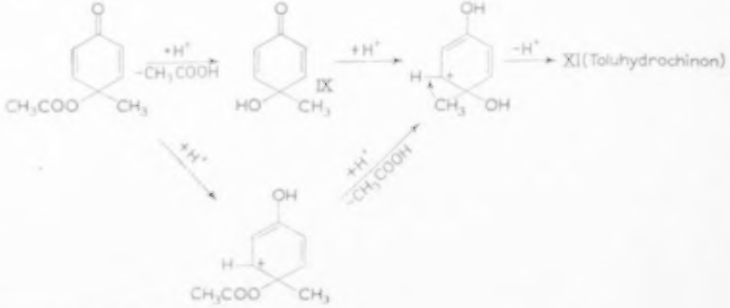


Auch diese Ergebnisse lassen sich durch die Konkurrenz zweier möglicher Reaktionen erklären:

(1) Interne Acetatwanderung, der die Verseifung des intermediär gebildeten Kresorcinmonoacetates folgt:



(2) Verseifung des Chinolacetates zum freien Chinol und anschliessende interne Methylwanderung oder Verseifung des primär gebildeten Kations mit anschliessender Methylwanderung:



[13] W. Lwowski, *Z. Angew. Chem.* **70**, 493 (1958).

Aus obigem Reaktionsschema folgt auch, dass IX bei der Behandlung mit Säuren quantitativ XI ergeben muss.

Abschliessend gibt Tabelle 1 eine Zusammenstellung der durchgeführten Umlagerungen und der erhaltenen Reaktionsprodukte. Reaktion α bedeutet Thieleacetylierung mit Acetanhydrid, Reaktion β desgleichen mit Diacetylsulfid, Reaktion γ Umlagerung unter Säure- bzw. BF_3-Katalyse.

TABELLE 1

Ausgangsstoff	Reaktion	Reaktionsprodukte	Bemerkungen
2-Methyl-*o*-chinolacetat[14]	α	2:6-Dihydroxytoluol (85%) + Toluhydrochinon (Spur)	3, a
	β	wie bei Reaktion α	a
2:3-Dimethyl-*o*-chinolacetat[15]	α	2:3-Xylohydrochinon	3
	β	wie bei Reaktion α + wenig I	a
2:6-Dimethyl-*o*-chinolacetat[16]	α	2:4-Dimethylresorcin	a
4-Methyl-*p*-chinolacetat	α	Kresorcin	a, vergl. 2
	β	wie Reaktion α	a
	γ	Kresorcin (Hptmenge) + Toluhydrochinon	a, vergl. 2
4-Methyl-*p*-chinol	α	Kresorcin (80%) + Toluhydrochinon (20%)	a, b vergl. 2
	β	wie bei Reaktion α + 30% XII	a
	γ	Toluhydrochinon	a
Mesityl-*p*-chinolacetat	α	Mesorcindiacetat + $C_{21}H_{28}O_6$	vergl. 3
Mesityl-*p*-chinol	α	wie bei dem Chinolacetat	a
4-Phenyl-*p*-chinolacetat	α	2:4-Dihydroxydiphenyl(82%) + 2:5-Dihydroxydiphenyl (Spur)	a
4-Phenyl-*p*-chinol	α	2:5-Dihydroxydiphenyl	11

a—Papierchromatographisch untersucht. b—Mengenverhältnis durch Schmelzdiagramm bestimmt.

EXPERIMENTELLER TEIL

A. *Allgemeines*

Dienon-Phenol-Umlagerung

Wenn nicht anders angegeben, setzten wir unter Rühren 0,15 g der fein gepulverten Chinolverbindung zu einem Gemisch von 1,5 ml Acetanhydrid bzw. Diacetylsulfid und drei Tropfen Borfluoridmethylätherat portionenweise unter eventueller Kühlung zu und liessen das Reaktionsgemisch 2 Std. bei Zimmertemperatur stehen. Bei den Umlagerungen in Acetanhydrid wurde das Reaktionsgemisch hierauf in Wasser gegossen und so über Nacht sich selbst überlassen. Die ausgefallenen Produkte filtrierten wir ab oder nahmen sie, wenn ölig, in Äther auf, um sie nach Entsäuern und Trocknen des Äthers durch Destillation zu reinigen. Bei Umlagerung in Diacetylsulfid wurde das Reaktionsprodukt sofort in Äther aufgenommen, dieser mit Bicarbonatlösung ausgeschüttelt und getrocknet. Die leichtflüchtigen Anteile (Lösungsmittel und überschüssiges

[14] W. Metlesics, E. Schinzel, H. Vilcsek, F. Wessely und *Mh. Chem.* **88**, 1069 (1957).
[15] F. Wessely, J. Kotlan und W. Metlesics, *Mh. Chem.* **85**, 69 (1954).
[16] G. W. K. Cavill, E. R. Cole, P. T. Gilham und D. J. McHugh, *J. Chem. Soc.* 2785 (1954).

Diacetylsulfid) wurden im Wasserstrahlvakuum bei 120° Badtemperatur entfernt, der Rückstand bei 0,1 Torr destilliert. Die weitere Aufarbeitung erfolgte, wie unten angegeben.

Verseifung der acetylierten Phenole. Verseift wurde mit Methanol–10proz. H_2SO_4 1 : 1 im Stickstoffstrom 4–6 Std. Nach Abdestillieren des Methanols im Vakuum wurde mit Äther ausgeschüttelt, die Ätherlösung entsäuert und getrocknet, der Äther abgedampft und der Rückstand bei 0,1 Torr im Kugelrohr destilliert.

Papierchromatographie der Phenole. Wir liessen die Substanzen mit der oberen Phase eines Gemisches von Benzol, Eisessig und Wasser im Verh. 4 : 1 : 5 absteigend laufen. Nach dem Trocknen des Papiers wurde mit einer wässrig-alkoholischen Lösung von diazotierter Sulfanilsäure besprüht und anschliessend mit Ammoniak geräuchert.

Abtrennung der Thiophenole. Das nach dem Verseifen durch Destillation gereinigte Phenolgemisch wurde in Äthanol gelöst und zu dieser Lösung $HgCl_2$ in 5proz. wässriger Lösung im Überschuss zugesetzt. Der gelblichweisse Niederschlag wurde abgesaugt und mit konz. HCl in der Kälte zersetzt. Das so freigesetzte Thiophenol wurde in Äther aufgenommen, die Ätherlösung mit Wasser und Bicarbonatlösung ausgeschüttelt, der Äther abgedampft und der Rückstand bei 0,1 Torr destilliert. Die so erhaltenen Kristalle wurden aus Petroläther umgelöst.

VOL. 6 1959

B. *Spezielles*

1. *Umlagerungen in Diacetylsulfid*

(a) 2-*Methyl*-o-*chinolacetat.* Nach dem Verseifen erhielten wir Kristalle, die nach Umlösen aus Benzol bei 119–121° schmolzen: 2:6-Dihydroxytoluol. In den Mutterlaugen konnte papierchromatographisch noch Toluhydrochinon nachgewiesen werden, hingegen ergaben sie keine Hg-Fällung.

(b) 2:3-*Dimethyl*-o-*chinolacetat.* Nach der Destillation des Reaktionsproduktes konnte durch Umlösen aus Äther reines 2:3-Dimethylhydrochinondiacetat erhalten werden. Die Mutterlaugen wurden verseift und durch Hg-Fällung das Thiophenol I erhalten (11% d. Th.). Schmp. 88–89°.

$C_8H_{10}OS$ Ber. C, 62,3 H, 6,5 S, 20,7

Gef. C, 62,0 H, 6,3 S, 19,9

Zum Vergleich der IR-Spektren wurde II aus 2:3-Dimethylphenolsulfonsäure-(4)[9] in Analogie zur Vorschrift von Karrer[8] durch Reduktion des Säurechlorides dargestellt. Schmp. 106°

$C_8H_{10}OS$ ber. S, 20,7 gef. S, 20,7

(c) 4-*Methyl*-p-*chinolacetat.* Das Umlagerungsprodukt wurde, wie angegeben, verseift. Das Papierchromatogramm zeigte nur einen Fleck von Kresorcin, Hg-Fällung konnte keine beobachtet werden.

(d) 4-*Methyl*-p-*chinol.* Das Papierchromatogramm des verseiften Umlagerungproduktes zeigte 3 Flecken, von denen 2 als Kresorcin und Methylhydrochinon identifiziert werden konnten. Durch Hg-Fällung wurde in 30 proz. Ausbeute ein Hydroxythiophenol vom Schmp. 47–49° (XII) isoliert.

C_7H_8OS Ber. C, 60,0 H, 5,8 S, 22,8

Gef. C, 60,6 H, 6,0 S, 23,4

Die Darstellung einer Vergleichssubstanz erfolgte durch Spalten des von Shah[17] dargestellten 2-Merkapto-4-methoxytoluols durch dreistündiges Kochen mit 10proz. HBr und Reinigung über das Hg-Salz. Von der von den Autoren angegebenen Synthese wichen wir bei der Darstellung der 4-Aminotoluolsulfonsäure-(2) ab, die wir durch Verseifen mit 10proz. NaOH und Äthanol im Verh. 1:1 des nach der Vorschrift von Johnson und Smiles[18] erhaltenen 4-Acetaminotoluolsulfonsäurechlorides-(2) darstellten. Das Vergleichspräparat und XII erwiesen sich durch Mischschmp. und Papierchromatogramm als identisch.

2. *Umlagerungen in Acetanhydrid*

(a) 2:6-*Dimethyl*-o-*chinolacetat.* Nach der entsprechenden Aufarbeitung erhielten wir 2:4-Dimethylresorcin (Schmp. und Mischschmp. 110–111°). Das Umlagerungsprodukt erwies sich als papierchromatographisch einheitlich.

[17] M. S. Shah, C. T. Bhatt, und D. D. Kanga, *J. Chem. Soc.* 1375 (1933).
[18] R. N. Johnson und S. Smiles, *J. Chem. Soc.* 2384 (1923).

(b) *Mesityl*-p-*chinolacetat*. Bei der entsprechenden Aufarbeitung wurden dieselben Reaktionsprodukte erhalten, die sich beim Mesityl-*o*-chinolacetat ergeben hatten,[3] nämlich Mesorcindiacetat (60%) und das Triacetat eines bisher nicht aufgeklärten Phenols $C_{15}H_{22}O_3$ (20%).

(c) *Mesityl*-p-*chinol*. Nach entsprechender Aufarbeitung konnten nur die unter (b) genannten Reaktionsprodukte nachgewiesen werden. Bei der papierchromatographischen Untersuchung der Verseifungsprodukte zeigte sich kein von Trimethylhydrochinon herrührender Fleck.

(d) 4-*Methyl*-p-*chinolacetat*. Das Papierchromatogramm des verseiften Umlagerungsproduktes zeigte nur einen Fleck von Kresorcin.

(e) 4-*Methyl*-p-*chinol*. Bei der papierchromatographischen Untersuchung des verseiften Reaktionsproduktes zeigten sich Flecken von Kresorcin und Methylhydrochinon. Das Verseifungsprodukt zeigte nach einmaligem Umlösen aus Benzol ein Schmelzintervall,[18] das etwa einem Mischungsverhältnis Kresorcin zu Toluhydrochinon 4 : 1 entspricht.

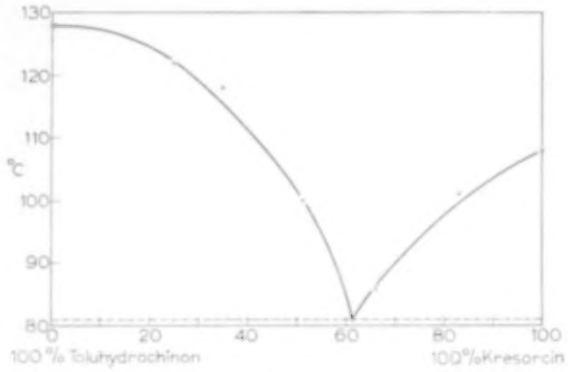


FIG. 1.

(f) 4-*Phenyl*-p-*chinolacetat*. Aus dem verseiften Umlagerungsprodukt konnte in 82proz. Ausbeute 2:4-Dihydroxydiphenyl erhalten werden, das durch Mischschmp. und Papierchromatogramm mit einem nach der Vorschrift von Smith[20] hergestellten Präparat identifiziert werden konnte. Das Papierchromatogramm der Mutterlaugen zeigte einen zweiten Fleck, der nach R_f-Wert und Farbreaktion dem Phenylhydrochinon entspricht.

Bei 4-Phenyl-*p*-chinolacetat und 4-Methyl-*p*-chinol erfolgte zur Kontrolle die Umlagerung unter H^+-Katalyse. Die Ergebnisse waren die gleichen wie bei Verwendung von BF_3.

3. *Säureumlagerungen*

(a) 4-*Methyl*-p-*chinolacetat*. Die Substanz wurde 3 Std. mit einem Gemisch von 10proz. H_2SO_4 und Methanol 1 : 1 unter Rückfluss gekocht. Das Papierchromatogramm zeigte Flecken von Kresorcin und Toluhydrochinon.

(b) 4-*Methyl*-p-*chinol*. Die Umlagerung erfolgte wie unter (a) angegeben. Das Papierchromatogramm zeigte nur einen Fleck von Toluhydrochinon.

Die Analysen wurden von Herrn Doz. Dr. Kainz im Mikrolabor des II. Chemischen Universitätsinstitutes durchgeführt.

Die IR-Spektren wurden auf einem IR-Spektrophotometer Perkin-Elmer 21 von Herrn Dr. J. Derkosch aufgenommen und interpretiert, wofür wir an dieser Stelle danken möchten.

[18] L. u. A. Kofler, *Thermomikromethoden*. Univ. Verlag Wagner, Innsbruck.
[20] P. G. Smith und C. M. Suter, *J. Amer. Chem. Soc.* **61**, 166 (1939).

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ASYMMETRIC ANNELLATION EFFECTS—II

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Abstract—The comparison of the U.V. absorption spectra of acenes, 1:2-3:4-dibenzacenes and tetrabenzacenes shows a strong asymmetric annellation effect. This is explained on the basic assumption that an aromatic sextet or benzenoid ring can transfer only two electrons to another ring. Three benzenoid rings can thus produce an induced aromatic sextet in an included ring of the type of the central ring in triphenylene.

The synthesis of tetrabenzotetracene is described.

VOL.
6
1959

IN the preceding communication[1] strong asymmetric annellation effects were reported in the series benzene I, triphenylene II and tetrabenzanthracene III. These were recorded in Å or better in $\sqrt{\text{Å}}$ the latter being a scale for reciprocal nuclear charges.[2] In order to eliminate the influence of the external benzene rings the second difference II → III was deducted from the β-band of triphenylene and it was found that the aromatic system of the central benzene ring was extended to a naphthalene system during the first annellation and that the second annellation produced an empty ring "E" only. From these facts it was deduced that a benzenoid ring containing three double bonds and six π-electrons and symbolised by a circle can transfer two electrons only to another ring as indicated by the arrows. Therefore only one induced benzenoid ring "Bz" can be formed.

If this interpretation is correct then the same principle should apply to the central acene system in a higher tetrabenzacene, without regard to the number of rings. There is only one benzenoid ring with an aromatic sextet in an acene independent of its length and accordingly only two transferable electrons. In order to prove this view the hitherto unknown tetrabenzotetracene VI was synthesised as described below. The annellation series napthalene IV, dibenzanthracene V[3] and tetrabenzotetracene VI also shows strong asymmetric shifts. The deduction of the second shift ($3{\cdot}57\sqrt{\text{Å}}$) from the β-band of dibenzanthracene V ($53{\cdot}48\sqrt{\text{Å}}$) gives $49{\cdot}91\sqrt{\text{Å}}$ or 2491 Å which is almost identical with the wavelength of the β-band of anthracene at 2515 Å as found in alcoholic solution or calculated by the annellation principle (2493 Å).[2]

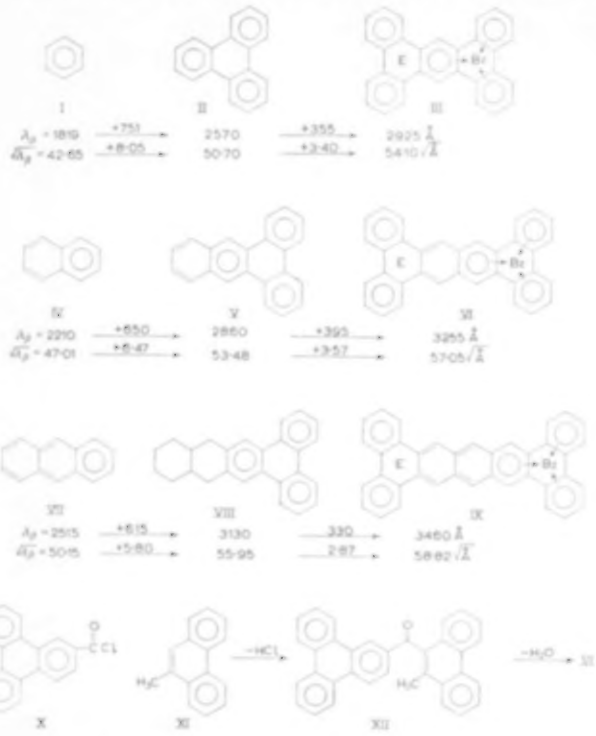
The conclusion is obvious that in the first annellation the aromatic structure of the central naphthalene system is extended to an anthracene system, whilst the second annellation produced an empty ring "E".

In the next higher series all three hydrocarbons, VII, VIII and IX[4] are known. The deduction of the second shift ($2{\cdot}87\sqrt{\text{Å}}$) from the β-band of 1:2-3:4-dibenzotetracene[5] VIII ($55{\cdot}95\sqrt{\text{Å}}$) yields a β-band at $53{\cdot}08\sqrt{\text{Å}}$ or 2818 Å. The β-band of tetracene is at 2740 Å in heptane solution. The calculation by the annellation principle[2] gives a β-band at 2802 Å. This comparison again indicates that in the first annellation the

[1] Part I: *Tetrahedron* **5**, 98 (1959).
[2] E. Clar, *Aromatische Kohlenwasserstoffe* p. 29. Springer Verlag (1952).
[3] E. Clar, *Ber. Dtsch. Chem. Ges.* **62**, 350, 1574 (1929).
[4] E. Clar, W. Kelly and W. G. Niven, *J. Chem. Soc.* 1833 (1956).
[5] E. Clar, *Ber. Dtsch. Chem. Ges.* **81**, 68 (1948).

aromatic system of anthracene is extended to a tetracene system as indicated by the arrows.

The idea of two π-electrons per aromatic sextet and benzenoid ring, capable of migrating through an acene system whilst the other π-electrons are confined to their rings is different from the quantum mechanical view of free movement of all π-electrons in molecular orbitals throughout the whole system. But it is in good agreement with the measurement of the diamagnetic anisotropy of the acenes which points to a high



degree of localisation of π-electrons in their rings. According to Akamatu and Matsunaga[6] this localisation increases with the number of linearly condensed rings. The average π-orbital radius (i.e. 1·71 Å for pentacene) is therefore much smaller than the length of the acene (about 12·14 Å for pentacene) would require, and increases to 1·94 Å for coronene and to 2·12 Å for ovalene.[6] The latter are systems with 3 and 4 benzenoid rings respectively and contain a triphenylene system with an induced benzenoid ring.[1]

The two transferable π-electrons are probably responsible for the addition of protons and for the different degree of basicity of aromatic hydrocarbons which reaches its extreme value in the azulenes.

Tetrabenzotetracene was synthesised from triphenylene-2-carboxylic acid,[9] the chloride of which was condensed with 9-methylphenanthrene[7] and aluminium chloride. The ketone XII was smoothly pyrolysed at 400° to tetrabenzotetracene VI.

[6] H. Akamatu and Y. Matsunaga, *Bull. Chem. Soc. Japan* **29**, 800 (1956).
[7] O. Kruber and A. Marx, *Ber. Dtsch. Chem. Ges.* **71**, 2478 (1938).

It has the lowest reactivity of all benzologues of tetracene. It reacts very slowly with boiling maleic anhydride to form a colourless adduct and does not dissolve in concentrated sulphuric acid. Unlike the other benzologues of tetracene it shows a yellow phosphorescence of considerable life in solid dioxan solution at −170°. In these properties it closely resembles the fully benzenoid hydrocarbons.[8] Its absorption spectrum is recorded in Fig. 1.

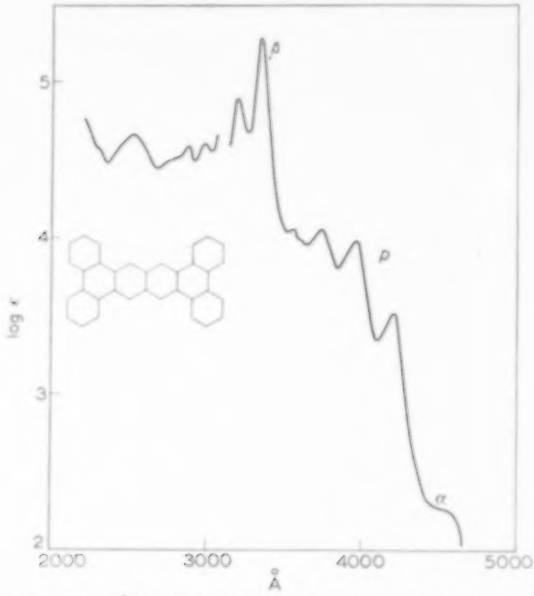


FIG. 1. Absorption max. (Å) and log ε (in parentheses). 1:2-3:4-8:9-10:11-Tetrabenzotetracene VI in trichlorobenzene, α: 4190 (3·50); *p*: 3960 (3·98), 3740 (4·06); β: 3340 (5·30), 3190 (4·90). In heptane, β: 3255 (5·30), 3120 (4·90), 2980 (4·60), 2880 (4·58); β′: 2530 (4·68).

EXPERIMENTAL*

1:2-3:4-8:9-10:11-*Tetrabenzotetracene* VI. The acid chloride (from 5·5 g of triphenylene-2-carboxylic acid[9] and thionyl chloride) was finely powdered and suspended in 200 ml of chlorobenzene. 9-Methylphenanthrene[2] (4 g) and aluminium chloride (3 g) were added and the mixture stirred at room temp for 4 hr. After heating at 50° for ½ hr the double compound was decomposed with ice and hydrochloric acid and the chlorobenzene removed by steam distillation. The ketone could not be obtained in a pure state from the yellow residue probably because of the formation of isomers which however could not cyclise in the following reaction. The ketone was dissolved in hot xylene, the solution dried, filtered and the xylene distilled off.

The ketone was pyrolysed at 400°. After ½ hr the elimination of water was complete and the residue was submitted to a vacuum sublimation at 400°/1 mm in a current of carbon dioxide. The first fraction yielded some triphenylene followed by yellow leaflets of *tetrabenzo*tetracene. This was twice recrystallised from 1:2:4-trichlorobenzene and formed yellow leaflets, m.p. 452–455° which did not dissolve in concentrated sulphuric acid but became green on the surface. The dilute solution in dioxan showed a phosphorescence of considerably long life after irradiation with a quartz lamp at −170°. (Found: C, 95·1; H, 4·8. $C_{34}H_{20}$ requires: C, 95·3; H, 4·7).

Acknowledgements—Microanalyses by Mr. J. M. L. Cameron and his staff, Glasgow University.

* Melting points are uncorrected and were taken in evacuated capillaries.

[8] E. Clar and M. Zander, *J. Chem. Soc.* 1861 (1958); E. Clar and C. T. Ironside, *Proc. Chem. Soc.* 150 (1958); E. Clar, M. Zander and C. T. Ironside, *J. Chem. Soc.* 142 (1959).

[9] J. W. Cook and C. L. Hewett, *J. Chem. Soc.* 401 (1933).

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ASYMMETRIC AND SYMMETRIC ANNELLATION EFFECTS—III*

BENZOCORONENES

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(*Received* 29 *December* 1958)

Abstract—1:2-5:6-Dibenzocoronene (IV) was obtained from 1:2-4:5-8:9-tribenzopyrene (II) via the dianhydride (III). 1:2-4:5-Dibenzopyrene (V) condensed twice with maleic anhydride. The resulting dianhydride (VI) gave 1:2-benzocoronene (VII) on decarboxylation. 1:12-*o*-Phenyleneperylene (X) was obtained by a zinc dust melt from the quinone (VIII). The annellation effects passing from triphenylene and perylene to the benzocoronenes indicate the presence of a triphenylene complex within the electronic fine structure of coronene.

2:3-8:9-DIBENZOPERYLENE (I) like other benzologues of perylene condenses with maleic anhydride and chloranil to form a new aromatic ring.[1] Giving this hydrocarbon the maximum number of aromatic sextets or benzenoid rings as indicated by the circles, the two central double bonds appear to be fixed. The above reaction might be related to this arrangement of double bonds. If this were the case then 1:2-4:5-8:9-tribenzopyrene (II) should also react with maleic anhydride and chloranil as a dehydrogenating agent. Although condensations of this type involving benzopyrenes have not been reported, tribenzopyrene (II) condensed twice in this way and yielded the dianhydride (III). Decarboxylation gave the pale yellow 1:2-5:6-dibenzocoronene (IV). Its absorption spectrum is recorded in Fig. 1 together with the tetrapotassium salt of the tetracarboxylic acid derived from (III).

An analogous formulation of the 1:2-4:5-dibenzopyrene (V) using aromatic sextets suggests the possibility of the same "benzenogenic" condensation. In accordance with this, dibenzopyrene (V) yielded the dianhydride (VI) from which 1:2-benzocoronene (VII)[2] was obtained by decarboxylation. The absorption spectra of both compounds (VI) and (VII) are reproduced in Fig. 2. It is remarkable that in these two cases of double benzenogenic condensations the number of benzenoid rings with inherent sextets increases by one and this might be the reason for the double condensation, since it would not be the case with a single condensation. When the crude adduct was examined after a short reaction, no dicarboxylic acid could be found in the absorption spectrum, indicating that the two molecules of maleic anhydride reacted simultaneously. For comparison of the annellation effects leading to the benzocoronene the unknown 1:12-*o*-phenyleneperylene (X) was needed. It was obtained from the quinone (VIII)[3] via the tetrahydro compound (IX)? by a zinc dust melt followed by a dehydrogenation. The spectra of (IX) and (X) are in Fig. 3.

* Part II: Tetrahedron **6**, 355 (1959).

[1] E. Clar, *Ber. Dtsch. Chem. Ges.* **65**, 846 (1932); *Chem. Ber.* **82**, 53 (1949); E. Clar and O. Kuhn, *Liebigs Ann.* **601**, 181 (1956); E. Clar, W. Kelly, J. M. Robertson and M. G. Rossmann, *J. Chem. Soc.* 3878 (1956); E. Clar, and M. Zander, *J. Chem. Soc.* 4616 (1957); 1861 (1958).

[2] E. Clar and M. Zander, *J. Chem. Soc.* 1577 (1958).

[3] F. Bergmann, H. E. Eschinazi and M. Neeman, *J. Org. Chem.* **8**, 179 (1943).

VOL.
6
1959

Coronene can be considered to be derived from triphenylene by connecting three double bonds to it with the formation of the three "empty" rings 1, 2, 3 in formula (XI). In this formula the central ring would have obtained induced benzenoid character by the reversible transfer of 3 π-electron pairs from the three benzenoid rings.[4] Another possibility is the hexagonally symmetric arrangement in formula (XII) in which the

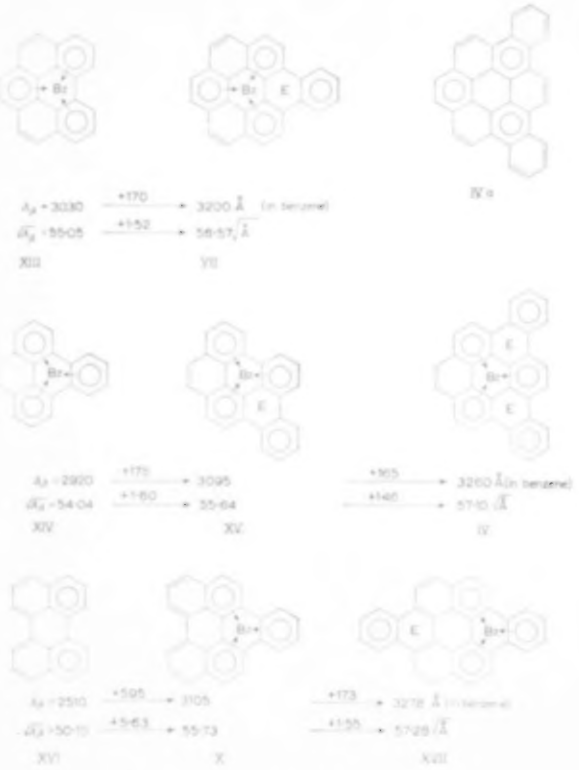
3 π-electron pairs are shared between neighbouring rings, thus forming three fused naphthalene systems. The central ring is here empty (E). Both formulae have the same number of inherent sextets in benzenoid rings, i.e. three.

Very significant spectral shifts of the β-bands accompany the connexion of the three double bonds to triphenylene as seen in formula (XI). The spectral shift due to the formation of the rings 1, 2 and 3 are 320, 100 and 30 Å corresponding to 3·06, 0·92 and 0·28 $\sqrt{\text{Å}}$. This is exactly contrary to what could be expected from the conventional ideas about aromaticity, namely, that the third double bond completing the external frame of nine conjugated double bonds should bring about the biggest shift. This external frame ought to allow a rotation of electrons through it. This is obviously not the case and neither does the effective π-orbital radius (1·94 Å) as

[4] E. Clar, *Tetrahedron* **5**, 98 (1959); **6**, 355 (1959).

obtained from the diamagnetic anisotropy measurements support this view.[5] In accordance with formula (XI) the three non-benzenoid double bonds in rings 1, 2 and 3 can be hydrogenated with the formation of 1:2-5:6-9:10-hexahydrocoronene.[6]

The building up of 1:2-benzocoronene (VII) from 1:12-benzoperylene (XIII) by an *o*-phenylene complex provides further support for formula (XI) for coronene. Since 1:12-benzoperylene already contains the stable triphenylene skeleton the effect of this annellation is small (170 Å, corresponding to $1{\cdot}52\sqrt{\text{Å}}$). This shift is well below the maximum value for two contact bonds and the newly formed ring must be empty. The same observation can be made when two *o*-phenylene radicals are attached to 1:2-benzopyrene (XIV) forming (XV) and (IV). The two shifts are similar to the one (XIII → VII).



1:2-Benzopyrene (XIV) also contains the triphenylene complex, so the double annellation produces two empty rings (E) and four contact bonds. If the triphenylene complex in 1:2-5:6-dibenzocoronene (IV) was free to rotate or oscillate through the coronene system the maximum number of five benzenoid rings would be reduced to three (formula IVa). Considering the extreme stability of hydrocarbons consisting exclusively of benzenoid rings this possibility seems remote. But this does not exclude an oscillation or rotation of the triphenylene complex in coronene itself.

[5] H. Akamatu and Y. Matsunaga, *Bull. Chem. Soc. Japan* **29**, 800 (1956).
[6] H. Fromherz, L. Thaler and G. Wolf, *Z. Elektrochem.* **49**, 387 (1943).

A strikingly different result is obtained when 1:2-7:8-dibenzocoronene (XVII) is built up from perylene in an analogous way. The first phenylene complex forms the triphenylene complex in (X). The shift related to it is far beyond the value for any pair of contact bonds (595 Å, corresponding to $5{\cdot}63\sqrt{\text{Å}}$). This process is therefore a benzenogenic annellation (Bz). The second phenylene complex in (XVII) produces two contact bonds (173 Å, corresponding to $1{\cdot}55\sqrt{\text{Å}}$) and an empty ring (E). The two naphthalene complexes forming the central perylene system have each, like any other acene, one pair of transferable π-electrons according to their definition given recently.[4] If an aromatic sextet is induced into the central ring of the triphenylene complex as indicated by the arrows in (XVII) then this process cannot be repeated simultaneously for the triphenylene system including the ring (E).

If the shift for the second annellation ($1{\cdot}55\sqrt{\text{Å}}$) is deducted from the β-band of 1·12-*o*-phenyleneperylene (X) a β-band at $54{\cdot}18\sqrt{\text{Å}}$ corresponding to 2936 Å is obtained. The β-band of 1·12-benzoperylene (XIII) is at 3030 Å for benzene solution. Although the agreement is not so close as in the case of the benzacenes described in the preceding paper it shows in the same way that the first annellation is a benzenogenic one (Bz) whilst the second produces an empty ring (E).

EXPERIMENTAL*

1:2-4:5-8:9-*Tribenzopyrene* (II). The method described by Zincke, Ott and Schuster[7] was modified in that stannic chloride was added. No unreacted picene was then recovered.

Picene (25 g), aluminium chloride (50 g) and stannic chloride (150 g) in benzene (250 ml) were refluxed for 2½ hr. The mixture was first blue and finally became violet red. After decomposition with hydrochloric acid and ice the tribenzopyrene (31 g) separated from the benzene layer and was filtered off. Vacuum sublimation yielded long needles (11·1 g).

1:2-5:6-*Dibenzocoronene*-7:8-11:12-*tetracarboxylic dianhydride* (III). Tribenzopyrene (II) (2.0 g), maleic anhydride (20 g) and chloranil (7.0 g) were refluxed for 1½ hr. The mixture was diluted with hot xylene, and the *dianhydride* (0·42 g) filtered off at room temp. A further 0·96 g dianhydride was obtained on concentration of the mother liquor. Dec. pt. >500°. An analytical sample was prepared by reprecipitation from alkali solution and refluxing with acetic anhydride. (Found: C, 77·0; H, 2·6. $C_{36}H_{14}O_7$ requires: C, 77·4; H, 2·5. $C_{36}H_{12}O_6$ requires: C, 80·0; H, 2·2%). The analysis fits the monoanhydride dicarboxylic acid rather than the dianhydride.

1:2-5:6-*Dibenzocoronene* (IV). The dianhydride (II) (4·0 g), potassium hydroxide (30 g) and water (100 ml) were heated in an autoclave for 18 hr at 350°. The crude product was washed with water and sublimed at 400°/0·05 mm. The sublimate crystallised from trichlorobenzene in long pale *yellow needles* (0·5 g). These had m.p. 327–328°C. and did not dissolve in concentrated sulphuric acid. (Found: C, 96·0; H, 4·1. $C_{32}H_{16}$ requires: C, 96·0; H, 4·0%). The spectra of (IV) and of the tetracarboxylic acid derived from (III) are shown in Fig.1.

1:2-*Benzocoronene*-3:4-7:8-*tetracarboxylic dianhydride* (VI). 1:2-4:5-Dibenzopyrene[8] (V) (30·2 g), chloranil (130 g) and maleic anhydride (200 g) were refluxed for 7 hr. Hot xylene (400 ml) was added and the precipitated *dianhydride* (18·7 g) filtered from the hot solution and washed with xylene and ether. Dec. pt. 460°. An analytical sample was prepared by reprecipitation and refluxing with acetic anhydride. (Found: C, 78·1; H, 2·4; $C_{32}H_{10}O_6$ requires: C, 78·4; H, 2·1%).

1:2-*Benzocoronene* (VII). The dianhydride (12·3 g), potassium hydroxide (35 g) and water (80 ml) were heated in an autoclave for 15 hr. The crude hydrocarbon was washed with water and sublimed at 300°/0·05 mm. Recrystallisation of the sublimate from xylene gave pale yellow needles (1·2 g).

* Melting points are uncorrected and were taken in evacuated capillaries.

[7] E. Clar, *J. Chem. Soc.* 2168 (1949); A. Zinke, R. Ott and O. Schuster, *Monat.* **83**, 1100, 1497 (1952).
[8] E. Clar, *Ber. Dtsch. Chem. Ges.* **73**, 609 (1943); I. G. Farbenindustrie A. G., French Patent 795447 (1935); B. Schiedt, *Ber. Dtsch. Chem. Ges.* **71**, 1248 (1938); A. Zinke and W. Zimmer, *Monat*, **81**, 783 (1950); A. Zinke and W. Zimmer, *Monat*, **82**, 348, 946 (1951).

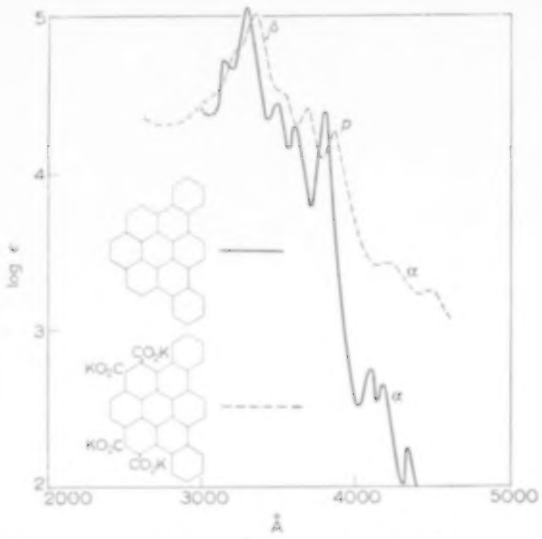


FIG. 1. Absorption max. (Å) and log ϵ (in parentheses).
1:2-5:6-Dibenzocoronene (IV) in $C_6H_5Cl_3$, α: 4335 (2·25), 4180 (2·66), 4100 (2·75); *p*: 3790 (4·38), 3600 (4·31), 3490 (4·45); β: 3280 (5·06), 3140 (4·72).
1:2-5:6-Dibenzocoronene-7:8-11:12-tetracarboxylic acid tetrapotassium salt in H_2O, α: 4470 (3·26), 4190 (3·43); *p*: 3850 (4·28), 3670 (4·39); β: 3345 (5·02).

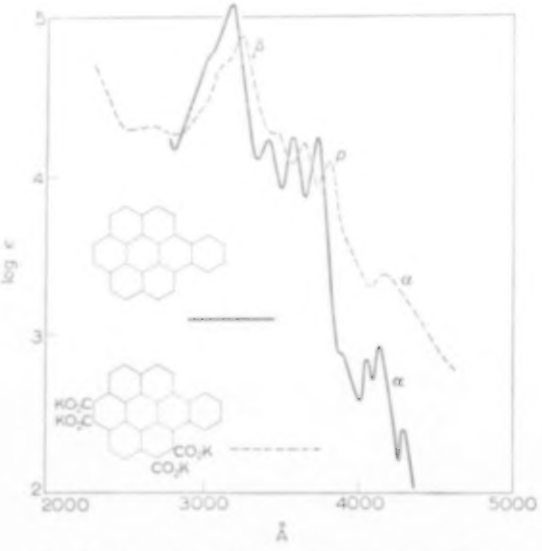


FIG. 2. Absorption max. (Å) and log ϵ (in parentheses).
1:2-Benzocoronene (VII) in C_6H_6, α: 4320 (2·50), 4140 (2·91), 4080 (2·85); *p*: 3760 (4·30), 3580 (4·30), 3430 (4·29); β: 3200 (5·15), 3080 (4·90). From 3000 Å in alcohol.
1:2-Benzocoronene-3:4-7:8-tetracarboxylic acid tetrapotassium salt in H_2O, α: 4190 (3·34); *p*: 3825 (4·06), 3650 (4·17), 3470 (4·26); β: 3260 (4·87).

The 1:2-benzocoronene had m.p. 292–294·5°, and gave no depression when mixed with the benzocoronene described recently.[2] The spectra of this hydrocarbon and of the tetracarboxylic acid from (VI) are shown in Fig. 2.

1:12-*o*-*Phenyleneperylene* (X). The quinone[3] (VIII) (0·6 g) was ground up with zinc dust (1·5 g) and sodium chloride (1·5 g) and melted with zinc chloride (7·5 g) and a few drops of water, with constant stirring. When the foaming subsided the temp was raised to 310° at which it was kept for 10 min. The colour changed to bright yellow. On extraction with benzene some crystals of (X) were

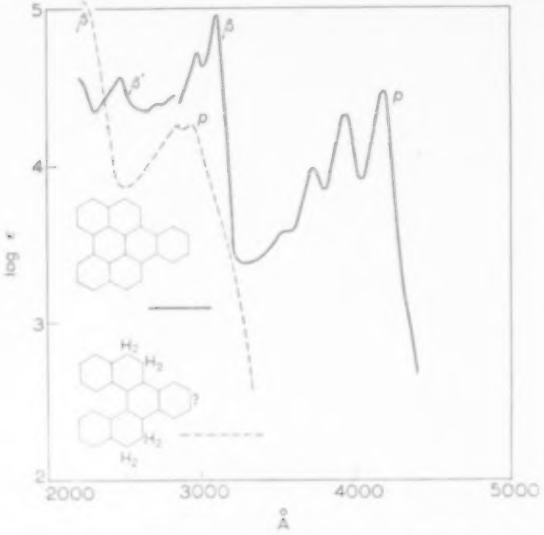


FIG. 3. Absorption max. (Å) and log ε (in parentheses).
1:12-*o*-Phenyleneperylene (X) in C_6H_6, *p*: 4180 (4·47), 3940 (4·31), 3730 (3·98), 3530 (3·58); *β*: 3105 (4·96), 2975 (4·74); in *cyclo*hexane, 2720 (4·40), *β'*: 2490 (4·56).
Tetrahydro-compound (IX)? in *cyclo*hexane, *p*: 2940 (4·26), 2840 (4·26).

obtained; however, when chromatographed on alumina, the mother liquor gave a trace of perylene identified spectroscopically and white plates of (IX)? The spectrum of this compound suggested a naphthalene derivative such as the *tetrahydro-compound* (IX) m.p. 148–149°C. though the analysis agreed better for a dihydro-compound. (Found: C, 94·6; H, 5·5. $C_{26}H_{18}$ requires: C, 94·5; H, 5·5. $C_{26}H_{20}$ requires: C, 93·9; H, 6·1%).

This hydro-compound which was quite stable, was dehydrogenated by passing over palladium charcoal at 350° to give 1:12-*o*-*phenyleneperylene* (X), which crystallised from benzene in long yellow needles, m.p. 268–270° (Found: C, 95·9; H, 4·3. $C_{26}H_{14}$ requires: C, 95·7; H, 4·3%). The spectra of (IX) and (X) are shown in Fig. 3. The hydro-compound (IX) showed strong yellow phosphorescence at −80°K in solid alcoholic *cyclo*hexane solution.

Phenyleneperylene, in accordance with the structure (X), reacted readily in the 6:7 position with boiling maleic anhydride and chloranil to form a red-brown anhydride, the spectrum of which showed it to be a derivative of 1:2 benzocoronene.

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VOL.
6
1959